# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205750Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

# EXCLUSIVITY SUMMARY

NDA # 205750 SUPPL # N/A HFD # 180

Trade Name Cholbam

Generic Name cholic acid

Applicant Name Asklepion Pharmaceuticals, LLC

Approval Date, If Known

**PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

b) If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

7

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

**PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

## PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If

the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently

demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 !
!
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in

interest provided substantial support for the study?

| | |
|---|---|
| Investigation #1 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

| | |
|---|---|
| Investigation #2 | ! |
| | ! |
| YES ☐ | ! NO ☐ |
| Explain: | ! Explain: |

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: CDR Anissa Davis-Williams
Title: Senior Regulatory Project Manager
Date:

Name of Office/Division Director signing form:
Title:

Form OGD-011347;  Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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BRIAN K STRONGIN
03/16/2015

ANDREW E MULBERG
03/16/2015

ASKLEPION
PHARMACEUTICALS, LLC

# FDA Debarment Certification Statement

Pursuant to Section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, Asklepion Pharmaceuticals, LLC, hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug and Cosmetic Act in connection with the Cholic Acid, NDA application (205,750).

Gary R. Pasternack, MD, PhD
Chief Executive Officer

18 Jun 2013
Date

729 East Pratt Street, Suite 360 · Baltimore, Maryland 21202
Office: (410) 545-0494 · Fax (410) 545-0584

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION[1]

| | | |
|---|---|---|
| NDA # 205750<br>BLA # n/a | NDA Supplement # n/a<br>BLA Supplement # n/a | If NDA, Efficacy Supplement Type: n/a<br>*(an action package is not required for SE8 or SE9 supplements)* |
| Proprietary Name: Cholbam<br>Established/Proper Name: cholic acid<br>Dosage Form: capsules | | Applicant: Asklepion Pharmaceuticals, LLC<br>Agent for Applicant (if applicable): n/a |
| RPM: CDR Anissa Davis-Williams/Brian Strongin | | Division: Division of Gastroenterology and Inborn Errors Products |

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

**For ALL 505(b)(2) applications, two months prior to EVERY action:**

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☒ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check: 3/13/15

***Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.***

| | |
|---|---|
| ❖ Actions | |
| • Proposed action<br>• User Fee Goal Date is 10/21/14 | ☒ AP ☐ TA ☐ CR |
| • Previous actions *(specify type and date for each action taken)* | ☒ None |
| ❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?<br>Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____ | ☐ Received |
| ❖ Application Characteristics[3] | |

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
***(confirm chemical classification at time of approval)***

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

| | |
|---|---|
| ❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter) | ☐ Yes, dates |
| ❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* | ☐ Yes ☐ No |
| ❖ Public communications *(approvals only)* | |
| • Office of Executive Programs (OEP) liaison has been notified of action | ☐ Yes ☐ No |
| • Indicate what types (if any) of information were issued | ☐ None<br>☒ FDA Press Release<br>☐ FDA Talk Paper<br>☐ CDER Q&As<br>☐ Other |
| ❖ Exclusivity | |
| • Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?<br>• If so, specify the type | ☒ No ☐ Yes |
| ❖ Patent Information (NDAs only) | |
| • Patent Information:<br>Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. | ☒ Verified<br>☐ Not applicable because drug is an old antibiotic. |

## CONTENTS OF ACTION PACKAGE

### Officer/Employee List

| | |
|---|---|
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)* | ☒ Included |
| Documentation of consent/non-consent by officers/employees | ☒ Included |

| | |
|---|---|
| **Action Letters** | |
| ❖ Copies of all action letters *(including approval letter with final labeling)* | Action(s) and date(s)<br>Approval/3-17-15 |
| **Labeling** | |
| ❖ Package Insert *(write submission/communication date at upper right of first page of PI)* | |
| • Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | ☒ Included 3-16-15 |
| • Original applicant-proposed labeling | ☒ Included 11/21/13 |
| ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* | ☐ Medication Guide<br>☐ Patient Package Insert<br>☐ Instructions for Use<br>☐ Device Labeling<br>☒ None |
| • Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)* | ☐ Included |
| • Original applicant-proposed labeling | ☐ Included |
| ❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)* | |
| • Most-recent draft labeling | ☒ Included (b) (4) |
| ❖ Proprietary Name<br>• Acceptability/non-acceptability letter(s) *(indicate date(s))*<br>• Review(s) *(indicate date(s)* | 2/20/14<br>Review- 2/11/14 |
| ❖ Labeling reviews *(indicate dates of reviews)* | RPM: ☐ None 1/11/14<br>DMEPA: ☐ None 2/16/14; 12/12/14<br>DMPP/PLT (DRISK): ☒ None<br>OPDP: ☐ None 3-6-15<br>SEALD: ☒ None<br>CSS: ☒ None<br>Other: ☒ None |
| **Administrative / Regulatory Documents** | |
| ❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* | 1/18/14 |
| ❖ All NDA (b)(2) Actions: 3-16-15 | ☐ Not a (b)(2) |
| ❖ NDAs only: Exclusivity Summary *(signed by Division Director)* | ☒ Included |
| ❖ Application Integrity Policy (AIP) Status and Related Documents<br>http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| • Applicant is on the AIP | ☐ Yes ☒ No |

[4] Filing reviews for scientific disciplines should be filed with the respective discipline.

| | |
|---|---|
| • This application is on the AIP<br>o If yes, Center Director's Exception for Review memo *(indicate date)*<br>o If yes, OC clearance for approval *(indicate date of clearance communication)* | ☐ Yes ☒ No<br>☐ Not an AP action |
| ❖ Pediatrics *(approvals only)*<br>• Date reviewed by PeRC _____<br>If PeRC review not necessary, explain: _____ | Not applicable; application is Orphan designated |
| ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters) *(do not include previous action letters, as these are located elsewhere in package)* | X |
| ❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes) | 4/23/14, 2/27/14, 1/30/14 |
| ❖ Minutes of Meetings | |
| • If not the first review cycle, any end-of-review meeting *(indicate date of mtg)* | ☒ N/A or no mtg |
| • Pre-NDA/BLA meeting *(indicate date of mtg)* | ☐ No mtg 7/29/13 (PDUFA V teleconference); 1/25/10 (Type B, Pre-NDA, clinical); 5/31/05 (Type B, pre-NDA CMC); 10/25/04 (Type B, Pre-NDA, development program) |
| • EOP2 meeting *(indicate date of mtg)* | ☒ No mtg |
| • Mid-cycle Communication *(indicate date of mtg)* | ☐ N/A 5/20/14 |
| • Late-cycle Meeting *(indicate date of mtg)* | ☐ N/A 9/19/14 |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)* | N/A |
| ❖ Advisory Committee Meeting(s) | ☒ No AC meeting |
| • Date(s) of Meeting(s) | n/a |
| **Decisional and Summary Memos** | |
| ❖ Office Director Decisional Memo *(indicate date for each review)* | ☐ None |
| Division Director Summary Review *(indicate date for each review)* | ☐ None |
| Cross-Discipline Team Leader Review *(indicate date for each review)* | ☐ None |
| PMR/PMC Development Templates *(indicate total number)* | ☐ None |
| **Clinical** | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| • Clinical review(s) *(indicate date for each review)* | 1/17/14; 3/11/15 |
| • Social scientist review(s) (if OTC drug) *(indicate date for each review)* | ☒ None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review<br>OR<br>If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)* | See 3/11/15 Clinical Review, page 14 |

| | |
|---|---|
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)* | ☐ None PMHS 2/24/15 and 12/15/14 |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)* | ☒ N/A |
| ❖ Risk Management<br>• REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))*<br>• REMS Memo(s) and letter(s) *(indicate date(s))*<br>• Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* | ☒ None |
| ❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)* | ☐ None requested 9/3/14 |
| **Clinical Microbiology** ☒ None | |
| ❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)* | ☐ No separate review |
| Clinical Microbiology Review(s) *(indicate date for each review)* | ☐ None |
| **Biostatistics** ☐ None | |
| ❖ Statistical Division Director Review(s) *(indicate date for each review)* | ☐ No separate review |
| Statistical Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| Statistical Review(s) *(indicate date for each review)* | ☐ None 1/17/14; 2/13/15; 3/12/15 |
| **Clinical Pharmacology** ☐ None | |
| Clinical Pharmacology Division Director Review(s) *(indicate date for each review)* | ☒ No separate review |
| Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)* | ☒ No separate review |
| Clinical Pharmacology review(s) *(indicate date for each review)* | ☐ None 1/17/14; 3/13/15 |
| ❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)* | ☐ None requested 1/21/14; 9/10/14; 9/26/14; 10/21/14; 12/10/14 |
| **Nonclinical** ☐ None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) *(indicate date for each review)* | ☒ No separate review |
| • Supervisory Review(s) *(indicate date for each review)* | ☒ No separate review |
| • Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)* | ☐ None 1/7/14; 7/30/14; 11/7/14 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)* | ☐ None |
| ❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)* | ☒ No carc |
| ❖ ECAC/CAC report/memo of meeting | ☐ None<br>Included in P/T review, page |
| ❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)* | ☐ None requested |

| **Product Quality** ☐ None | |
|---|---|
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) *(indicate date for each review)* | ☐ No separate review |
| • Branch Chief/Team Leader Review(s) *(indicate date for each review)* | ☐ No separate review 1/15/14 (CMC filing review); 8/4/14 and 2/24/15 |
| • Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)* | ☐ None 1/15/14 (Biopharm Filing Review; Biopharm Review 7/24/14 and 12/5/14 |
| ❖ Microbiology Reviews<br>☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)*<br>☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)* | ☐ Not needed<br>12/4/13 |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)* | ☐ None 1/9/14 (ONDQA/CGMP filing review) |
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| ☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)* | 8/4/15 Product Quality Review (see page 77) |
| ☐ Review & FONSI *(indicate date of review)* | |
| ☐ Review & Environmental Impact Statement *(indicate date of each review)* | |
| ❖ Facilities Review/Inspection | |
| ☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within **2 years** of action date) *(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[5])* | Date completed: 9/10/14 and 9/26/14<br>☒ Acceptable<br>☐ Withhold recommendation<br>☐ Not applicable |
| ☐ BLAs: TB-EER (date of most recent TB-EER must be within **30 days** of action date) *(original and supplemental BLAs)* | Date completed:<br>☐ Acceptable<br>☐ Withhold recommendation |
| ❖ NDAs: Methods Validation *(check box only, do not include documents)* | ☒ Completed (6/16/14 and 9/25/14)<br>☐ Requested<br>☐ Not yet requested<br>☐ Not needed (per review) |

[5] i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

| Day of Approval Activities | |
|---|---|
| ❖ For all 505(b)(2) applications:<br>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) | ☒ No changes<br>☐ New patent/exclusivity *(Notify CDER OND IO)* |
| • Finalize 505(b)(2) assessment | ☒ Done |
| ❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email | ☒ Done |
| ❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter | ☒ Done |
| ❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name | ☒ Done |
| ❖ Ensure Pediatric Record is accurate | ☒ Done |
| ❖ Send approval email within one business day to CDER-APPROVALS | ☒ Done |

## Davis, Anissa

**From:** Dimick, Lara L
**Sent:** Thursday, March 12, 2015 8:53 AM
**To:** Gary Pasternack; 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Cc:** Beitz, Julie G; Strongin, Brian K; Davis, Anissa; Mulberg, Andrew; Gao, Wen-Yi
**Subject:** RE: Request for Clarification - NDA 205750

Kellie and Gary,

In response to your questions our answers are in black. I believe there are no other outstanding issues. Please redo the numbers in section 14, based on these responses and send this by e-mail by close of business today. Please let us know if you have any questions.

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Thank you,

*Lara*
*Lara Dimick-Santos, MD*
*Medical Team Leader*
*Liver and Inborn Errors of Metabolism Team*
*FDA/CDER/OND/ODE3/DGIEP*
*White Oak - Building 22, Room 5327*

*O - 301-796-4843*
*M -* (b) (6)
*Lara.Dimick@fda.hhs.gov*

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Wednesday, March 11, 2015 4:30 PM
**To:** Dimick, Lara L
**Cc:** Beitz, Julie G; Strongin, Brian K; Davis, Anissa; 'Kellie Kennon'
**Subject:** Request for Clarification - NDA 205750
**Importance:** High

Dear Dr Dimick,

We have conducted a preliminary review of the Information Request of March 11, 2015 (included below with attachments) and believe that we need some clarification before we can respond. In conducting the responder analysis, we strictly applied the FDA responder criteria as outlined by FDA in the document entitled "JBs Proposed Agenda for the 11-18-14 T-Con with Sponsor Final 11-14-14":

> …Response was assessed by the following laboratory criteria: (1) ALT or AST values reduced to <50 U/L, or baseline levels reduced by 80%; (2) total bilirubin values reduced to ≤ 1 mg/dL; and (3) no evidence of cholestasis on liver biopsy, and the following clinical criteria: (1) body weight increased by 10% or stable at > 50$^{th}$ percentile; and (2) alive at the last follow-up.
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> Cholbam responders were defined as patients who either (1) met at least two of the laboratory criteria and were alive at the last follow-up; or (2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

When we compare the foregoing criteria to the criteria applied in the FDA tables received today entitled "Analysis of sponsor's responder analysis for cholic acid" and "NDA 205-750 PD final responder list", we note some ambiguities that we would like the Agency to clarify. As written, the criteria simply require that the patient was alive at the last follow-up but do not specify a required threshold length of follow-up. However, in the SED group, patient 024 was considered a non-responder by FDA because, although alive at last follow-up, the Reviewer did not consider the length of follow-up to be adequate. Similarly, in the PD group, patients 173, 032, and 035 meet FDA criteria for response, but the Reviewer has counted these patients as non-responders because survival data, although meeting the criterion of being alive at last follow-up, were judged to be inadequate by the Reviewer.

In view of the above ambiguity regarding the survival criterion, we ask the Agency for the following clarifications:

1. Does the Agency wish to modify the responder criteria to include a minimum documented survival time, and, if so, what survival time does the Agency wish to apply?
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We look forward to providing a substantive response once the Agency clarifies these points. Since the response will entail redoing statistical output, we will not be able to respond by the close of business tomorrow as requested by CDR Davis-Williams. Once we receive your views, we will be better able to forecast the timing of the response.

Sincerely

Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

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729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



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**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Wednesday, March 11, 2015 1:28 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** kellie.kennon@asklepionpharm.com; Strongin, Brian K
**Subject:** NDA 205750: Clinical Information Request
**Importance:** High

Hello Dr. Pasternack:

**We disagree with the following responders that you have included in your responder analysis. The differences in our responder analysis methods appear to be:**

1. We are using "last value before treatment" as a baseline (b) (4) (Note: we are both using "best" post-baseline value). You should adjust your analysis to use the last pre-baseline value.

2. At times there is no baseline before treatment and the baseline was established shortly after treatment was started. I have highlighted and explained when this was deemed clinically reasonable in the responder analysis list.

3. [redacted] (b) (4)
We count only patients with abnormal baseline values as responders. You need to [redacted] (b) (4) include patients as responders in bilirubin and transaminases who had elevated baseline values.

4. You have labeled patients [redacted] (b) (4) We do not agree that that is appropriate in this disease and those patients should be labeled as non-survivors. In addition, if patients survived off treatment for many years they cannot be counted as treatment responders.

**Therefore we do not list the following patients as responders:**

SED:
024, 074, 149 and 027

PD:
173, 007, 032 and 035

**We do include PD patient 021 as a responder in trial 2**
PD patient 51 is technically a responder however it is not clear that she required or benefited from treatment.

**See attached lists of responders with comments.**

*Please provide your response officially to your application by close of business tomorrow, March 12, 2015.*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ANISSA A DAVIS
03/12/2015

## Davis, Anissa

**From:** Dimick, Lara L
**Sent:** Thursday, March 12, 2015 12:57 PM
**To:** Kellie Kennon
**Cc:** Beitz, Julie G; Strongin, Brian K; Davis, Anissa; Mulberg, Andrew; Gao, Wen-Yi; Gary Pasternack; Gemma Hodgson
**Subject:** RE: NDA 205750 - Responder Analysis (Revision per FDA email 11Mar2015)

I think alive 3 years or alive at the end-of- trial 2 as a definition should be adequate, since trial 2 data is less than 3 years and we have excluded the patients who were only in the trial briefly I think we can continue to count all the treatment naïve pts in trial 2 as survivors and responders as previously noted (5 SED, 1 PD), and all patients in trial 1 who survived greater than 3 years on treatment can be counted as survivors.

Please send the revised numbers for section 14 by total "evaluable mITT" and responders total and by subtype as soon as you have the numbers. I will make the changes to the PI here, but want to verify that we have the same numbers. If you have made the changes to section 14 you can send that to me ASAP, I would appreciate it, I will enter the changes in the PI.

*Lara*

*Lara Dimick-Santos, MD*
*Medical Team Leader*
*Liver and Inborn Errors of Metabolism Team*
*FDA/CDER/OND/ODE3/DGIEP*
*White Oak - Building 22, Room 5327*
*O - 301-796-4843*
*M -* (b) (6)
*Lara.Dimick@fda.hhs.gov*

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**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Thursday, March 12, 2015 12:14 PM
**To:** Dimick, Lara L
**Cc:** Beitz, Julie G; Strongin, Brian K; Davis, Anissa; Mulberg, Andrew; Gao, Wen-Yi; Gary Pasternack; Gemma Hodgson
**Subject:** NDA 205750 - Responder Analysis (Revision per FDA email 11Mar2015)
**Importance:** High

Good afternoon Lara,

We have reviewed your comments and made the necessary changes to the responder analysis. I have forwarded the data to our statistical team, but I'm not certain they will have the tables and listings available before COB today. Therefore, I have provided the responder analysis data in the attached. I will forward the tables/listings as soon as they are available and follow-up with a formal submission to the NDA.

Additionally, I have made revisions to Section 14 that reflect the changes in the attached. I can either submit those to you via email now or await further input from you regarding the definition of survival as that may impact the figures we have in our label now.

Currently, we have defined survival as being alive at least 3 years post treatment start. If this changes, I may have to review the figures for accuracy. Please advise whether you'd care for the PIs in their current form or if I should wait for further instruction.

Many thanks,
Kellie

Kellie A. Kennon, BSN | Senior Director of Clinical Research |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

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**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Thursday, March 12, 2015 11:42 AM
**To:** 'Dimick, Lara L'; Kellie Kennon
**Cc:** 'Beitz, Julie G'; 'Strongin, Brian K'; 'Davis, Anissa'; 'Mulberg, Andrew'; 'Gao, Wen-Yi'
**Subject:** RE: Request for Clarification - NDA 205750

Lara,

Thanks very much for the quick turnaround and helpful comments. We've been working on this since the arrival of your e-mail this morning. Kellie will be back to you later today with the timing of the submission.

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
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**From:** Dimick, Lara L [mailto:Lara.Dimick@fda.hhs.gov]
**Sent:** Thursday, March 12, 2015 8:53 AM

**To:** Gary Pasternack; 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Cc:** Beitz, Julie G; Strongin, Brian K; Davis, Anissa; Mulberg, Andrew; Gao, Wen-Yi
**Subject:** RE: Request for Clarification - NDA 205750

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Gary Pasternack

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**Sent:** Wednesday, March 11, 2015 1:28 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** kellie.kennon@asklepionpharm.com; Strongin, Brian K
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*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

| PID | PrimaryDiagnosis | Baseline ALT | Baseline AST | Responder |
|---|---|---|---|---|
| 0 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | - | - | UNK |
| 1 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 243 | 250 | NO |
| 7 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 142 | 203 | YES |
| 9 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 59 | 73 | YES |
| 11 | Peroxisomal Biogenesis Disorder: Zellwegers | 75 | 1317 | UNK |
| 12 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 312 | 470 | YES |
| 13 | Peroxisomal Biogenesis Disorder: Type unknown | 276 | 393 | YES |
| 16 | Cholesterol 7 α-hydroxylase (CYP7A1) | - | - | UNK |
| 17 | Peroxisomal Biogenesis Disorder: Zellwegers | 307 | 505 | UNK |
| 18 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | - | - | NO |
| 19 | Peroxisomal Biogenesis Disorder: Zellwegers | 200 | 546 | NO |
| 20 | Peroxisomal Biogenesis Disorder: Refsum's | 119 | 320 | YES |
| 21 | Peroxisomal Biogenesis Disorder: Refsum's | 72 | 78 | NO |
| 24 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 51 | 55 | NC |
| 27 | Sterol 27-hydroxylase (CTX) | - | - | UNK |
| 29 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 69 | 139 | UNK |
| 30 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 119 | 148 | YES |
| 31 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 39 | 44 | NO |
| 32 | Peroxisomal Biogenesis Disorder: Zellwegers | 132 | 360 | YES |
| 33 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 58 | 49 | YES |
| 34 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 92 | 135 | YES |
| 35 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 98 | 270 | NC |
| 36 | Peroxisomal Biogenesis Disorder: Zellwegers | 32 | 66 | YES |
| 37 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 374 | 1080 | NO |
| 40 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 248 | 247 | No |
| 46 | Peroxisomal Biogenesis Disorder: Zellwegers | 56 | 86 | YES |
| 47 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 298 | 264 | YES |
| 51 | Peroxisomal Biogenesis Disorder: Type unknown | 18 | 68 | YES |
| 55 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 150 | 115 | NO |
| 56 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 54 | 86 | NO |
| 57 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 505 | 871 | YES |
| 59 | Peroxisomal Biogenesis Disorder: Zellwegers | 249 | 431 | UNK |
| 64 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 90 | 135 | YES |
| 65 | Sterol 27-hydroxylase (CTX) | 422 | 481 | YES |
| 68 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | 590 | 668 | YES |
| 69 | Peroxisomal Biogenesis Disorder: Neonatal Adrenoleukodystrophy | 22 | 44 | NO |
| 72 | Peroxisomal Biogenesis Disorder: Refsum's | 204 | 667 | NO |
| 73 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 418 | 588 | NC |
| 74 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 50 | 38 | NO |
| 75 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | - | - | UNK |
| 76 | 2- (or α-) methylacyl-CoA racemase (AMACR) | 223 | 199 | YES |

| | | | | |
|---|---|---|---|---|
| 78 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 67 | 118 | UNK |
| 79 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 48 | 101 | YES |
| 80 | Peroxisomal Biogenesis Disorder: Zellwegers | 102 | 444 | NO |
| 83 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 89 | 85 | NO |
| 86 | Sterol 27-hydroxylase (CTX) | 99 | - | YES |
| 87 | Peroxisomal Biogenesis Disorder: Type unknown | 20 | 37 | YES |
| 90 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 41 | 54 | YES |
| 91 | Peroxisomal Biogenesis Disorder: Type unknown | 33 | 74 | NC |
| 92 | Peroxisomal Biogenesis Disorder: Generalized Peroxisomal Disorder | 83 | 130 | NO |
| 93 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 398 | 305 | YES |
| 95 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 921 | 967 | YES |
| 100 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 354 | 676 | YES |
| 102 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | 284 | 487 | YES |
| 103 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | 315 | 820 | NO |
| 105 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | - | - | UNK |
| 106 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 118 | 145 | YES |
| 107 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 60 | - | YES |
| 123 | Peroxisomal Biogenesis Disorder: Zellwegers | - | - | UNK |
| 127 | Smith-Lemli-Opitz | - | - | UNK |
| 128 | Peroxisomal Biogenesis Disorder: Refsum's | 396 | 449 | YES |
| 130 | Peroxisomal Biogenesis Disorder: Type unknown | 462 | 526 | NO |
| 132 | Peroxisomal Biogenesis Disorder: Zellwegers | 282 | 639 | YES |
| 133 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | 154 | 191 | YES |
| 134 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | - | - | UNK |
| 138 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 68 | 73 | YES |
| 142 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 129 | 192 | YES |
| 143 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 1094 | 1080 | NO |
| 145 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 120 | 92 | YES |
| 149 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 39 | 50 | NC |
| 152 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | - | - | UNK |
| 153 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | - | - | NO |
| 156 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | - | - | NO |
| 157 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 308 | 291 | YES |
| 159 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 82 | 103 | NO |
| 173 | Peroxisomal Biogenesis Disorder: Zellwegers | 178 | 504 | YES |
| 175 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 58 | 77 | YES |
| 177 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 20 | 60 | YES |
| 193 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | - | - | UNK |
| 176 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 126 | 109 | YES |
| 700 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 150 | 202 | YES |
| 701 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | | | |
| 702 | Peroxisomal Biogenesis Disorder: Zellwegers | | | |
| 703 | Peroxisomal Biogenesis Disorder: Zellwegers | 165 | 290 | YES |
| 704 | Δ4-3-oxosteroid 5β-reductase (Δ4-3-oxo-R or AKR1D1) | | | |
| 705 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 43 | 51 | YES |
| 706 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 106 | 91 | YES |
| 707 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | 41 | 71 | YES |
| 708 | Sterol 27-hydroxylase (CTX) | | | |

| | | | | |
|---|---|---|---|---|
| 709 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | | | |
| 710 | Unconfirmed Defect Type | | | |
| 711 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | | | |
| 712 | Sterol 27-hydroxylase (CTX) | | | |
| 713 | 3β-hydroxy-Δ5-C27-steroid oxidoreductase | | | |

Note: NE = not evaluable, NC = non-contributory, NA = not applicable and UNK = unknown

| Lab Criteria | | | | | Clinical Criteria | | |
|---|---|---|---|---|---|---|---|
| Baseline Bilirubin | Responder | Prothrombin Time (CAC-002-01 only) | PT Responder (CAC-002-01 only) | Cholestasis (91-10-10 only) | Baseline Weight | Responder | Alive |
| - | UNK | | | UNK | - | UNK | NO |
| 6.77 | NO | | | UNK | 3.60 | NO | YES |
| 0.70 | NO | | | NC | 10.69 | NC | YES |
| 4.39 | NO | | | UNK | 15.30 | YES | YES |
| 0.70 | UNK | | | UNK | 3.54 | YES | YES |
| 0.80 | YES | - | NC | UNK | 3.49 | YES | YES |
| - | NO | | | UNK | 3.20 | YES | NO |
| - | UNK | | | UNK | - | UNK | NO |
| 7.80 | UNK | | | UNK | 3.66 | UNK | NO |
| - | NO | | | UNK | - | NO | YES |
| - | NO | | | UNK | 2.92 | UNK | NO |
| 0.60 | YES | - | UNK | UNK | 9.28 | YES | YES |
| 0.10 | YES | - | UNK | UNK | 11.30 | YES | YES |
| - | NO | | | UNK | 7.00 | YES | YES |
| - | UNK | - | NC | UNK | - | UNK | YES |
| - | UNK | | | UNK | 4.30 | NC | NO |
| 1.40 | YES | - | UNK | UNK | 9.60 | NO | YES |
| 1.52 | YES | | | NC | 50.20 | NO | YES |
| 1.50 | NC | | | NO | 3.60 | NC | YES |
| 0.90 | NO | - | UNK | UNK | 33.50 | YES | YES |
| 10.20 | YES | - | UNK | UNK | 32.10 | NC | YES |
| 6.14 | YES | | | UNK | 8.50 | NC | YES |
| 0.40 | NO | | | NO | 3.49 | YES | NO |
| 1.30 | NC | | | NO | 4.20 | YES | NO |
| 1.64 | NO | | | UNK | 3.70 | NO | YES |
| 0.30 | YES | - | NC | UNK | 3.77 | YES | YES |
| 1.93 | YES | | | UNK | 12.80 | YES | YES |
| 0.30 | NC | | | UNK | 26.70 | YES | YES |
| 1.46 | NO | | | UNK | 25.00 | NO | YES |
| 1.93 | NO | | | UNK | 13.20 | NO | YES |
| 17.50 | YES | - | NC | UNK | - | YES | NO |
| 0.30 | UNK | | | UNK | 2.58 | UNK | NO |
| 0.40 | NC | | | UNK | 8.00 | YES | YES |
| 6.40 | YES | - | NC | NO | 2.39 | YES | YES |
| 15.00 | YES | - | NC | UNK | 9.53 | NC | YES |
| - | NO | | | UNK | 3.70 | YES | NO |
| - | NO | | | UNK | 6.80 | NO | NO |
| 2.80 | NO | | | UNK | 33.00 | YES | YES |
| 1.41 | YES | | | UNK | - | NO | YES |
| - | UNK | | | UNK | - | UNK | YES |
| 4.20 | YES | | | YES | 3.37 | YES | YES |

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|---|---|---|---|---|---|---|---|
| 5.79 | UNK | | | UNK | 12.60 | UNK | YES |
| 0.70 | YES | - | NC | UNK | 12.20 | YES | YES |
| 10.90 | NO | | | UNK | 5.50 | NO | NO |
| 92.00 | NO | | | UNK | - | NO | YES |
| 22.80 | YES | - | NO | UNK | - | YES | YES |
| 1.70 | YES | | | NC | 2.58 | NC | NO |
| 1.20 | YES | - | NC | UNK | 15.00 | NC | YES |
| - | NO | | | UNK | 11.20 | UNK | NO |
| 0.30 | YES | - | NC | UNK | 12.06 | YES | YES |
| - | YES | - | NC | NO | 8.00 | YES | YES |
| 13.50 | YES | - | NC | UNK | 6.67 | YES | YES |
| 1.40 | YES | - | NC | UNK | 6.10 | YES | YES |
| - | YES | | | UNK | 5.10 | YES | YES |
| 21.40 | NO | | | UNK | 7.10 | UNK | NO |
| - | UNK | | | UNK | - | UNK | YES |
| 3.50 | YES | - | NC | UNK | 10.09 | YES | YES |
| 3.88 | YES | | | UNK | 38.50 | UNK | YES |
| - | UNK | | | UNK | - | UNK | NO |
| - | UNK | | | UNK | - | UNK | YES |
| - | UNK | - | NO | UNK | 10.40 | YES | YES |
| - | NO | - | NO | UNK | 3.23 | YES | NO |
| - | NO | - | NO | UNK | 3.03 | NO | YES |
| 0.01 | YES | - | NC | UNK | 4.49 | YES | YES |
| - | UNK | | | NC | - | UNK | YES |
| 2.30 | YES | - | NC | UNK | - | YES | YES |
| 0.17 | NO | | | NC | - | NO | YES |
| - | NO | | | UNK | 8.50 | UNK | NO |
| 1.00 | YES | - | NC | UNK | 7.80 | YES | YES |
| 0.70 | NO | - | NC | UNK | 11.00 | YES | YES |
| - | UNK | | | UNK | - | UNK | NO |
| - | NO | | | UNK | - | NO | YES |
| - | NO | | | UNK | 31 | UNK | YES |
| 7.31 | YES | - | UNK | UNK | - | YES | YES |
| 5.90 | NO | - | NC | UNK | 13.30 | YES | YES |
| 4.80 | UNK | - | UNK | UNK | 5.00 | NC | YES |
| 3.20 | YES | - | UNK | UNK | 75.70 | NO | YES |
| 10.30 | YES | - | UNK | UNK | - | NO | YES |
| - | UNK | | | UNK | - | UNK | YES |
| 0.60 | YES | - | NC | | 25.00 | YES | YES |
| 5.80 | YES | - | NC | | | NO | YES |
| | | | | | | | |
| | | | | | | | |
| 3.30 | YES | - | UNK | | 3.90 | YES | YES |
| | | | | | | | |
| 0.70 | YES | - | NC | | 7.00 | YES | YES |
| 2.39 | YES | - | NC | | 13.00 | YES | YES |
| 0.92 | YES | - | NC | | 15.80 | YES | YES |
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| **Responder in 91-10-10** | **Responder in CAC-002-01** | **Overall Responder** |
| | | NE |
| NO | NA | NO |
| NO | NA | NO |
| YES | NA | YES |
| NO | NA | NO |
| YES | YES | YES |
| NO | NA | NO |
| | | NE |
| | | NE |
| NO | NA | NO |
| NO | NA | NO |
| YES | YES | YES |
| NC | YES | YES |
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| YES | NE | YES |
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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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ANISSA A DAVIS
03/12/2015

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Wednesday, March 11, 2015 1:28 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'kellie.kennon@asklepionpharm.com'; Strongin, Brian K
**Subject:** NDA 205750: Clinical Information Request

**Importance:** High

Hello Dr. Pasternack:

**We disagree with the following responders that you have included in your responder analysis. The differences in our responder analysis methods appear to be:**

1) We are using "last value before treatment" as a baseline (b) (4) (Note: we are both using "best" post-baseline value). You should adjust your analysis to use the last pre-baseline value.

2) At times there is no baseline before treatment and the baseline was established shortly after treatment was started. I have highlighted and explained when this was deemed clinically reasonable in the responder analysis list.

3) (b) (4) You need to (b) (4) include patients as responders in bilirubin and transaminases who had elevated baseline values.

4) (b) (4) We do not agree that that is appropriate in this disease and those patients should be labeled as non-survivors. In addition, if patients survived off treatment for many years they cannot be counted as treatment responders.

**Therefore we do not list the following patients as responders:**

SED:
024, 074, 149 and 027

PD:
173, 007, 032 and 035

**We do include PD patient 021 as a responder in trial 2**
PD patient 51 is technically a responder however it is not clear that she required or benefited from treatment.

**See attached lists of responders with comments.**


*Please provide your response officially to your application by close of business tomorrow, March 12, 2015.*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

Analysis of sponsor's responder analysis for cholic acid

**SED**

009 – Responder (*weight baseline one month after tx. start)
024 - I disagree that this is a responder– he is technically a responder on AST with a baseline of 55, but normal baseline bili. Treated only 1 year then lost to f/u. did respond on weight. I would tend to say no because we do not have survival beyond 1 year documented
033 – Responder
034 – Responder
047- Responder
057 – Responder (*baseline day 90)
065- Responder (*in trial 2)
068- Responder
074 – not a responder as baseline bilirubin and transaminases both normal. Was 10 years old at start of treatment and no weight data recorded. Only meets survival and not clear that treatment was needed.
079- Responder
086- Responder
090- Responder
093- Responder
095- Responder
100- Responder
102- Responder
106- Responder
107 – Responder (*baseline for bilirubin and date of start of treatment unclear)
133 – Responder
145 – Responder (*in trial 2)
149 – Not a responder as normal baseline TB/AST/ALT had only survival and weight (*baseline and treatment dates imputed)
157 – Responder (*start of treatment date imputed from shipping logs)
175- Responder
076- Responder
027 – Not a responder as baseline TB/AST/ALT normal
138 – Responder (*no baseline weight, but 7 year survivor and grew with weight data in trial 2)
176- Responder
700- Responder
705- Responder
706- Responder
707- Responder

Note:

177 –This is not a responder per Asklepion. And I agree, no baseline labs. Normal AST/ALT/TB during trials

NDA 205-750 PD final responder list:

030 – Responder
128 – Responder (*Trial 2[T2])
132—Responder (expired in T2 due to unrelated cause, weight data in T2)
173 – Not a responder, only treated 1+ year and survival unknown, had steatorrhea pre-tx no documentation post-tx (started treatment at the very end of Trial 1, so technically was a survivor at the end of T1 and continued into T2, but only treated about one year and then consent withdrawn and no further data. Did respond with ALT, but not AST and no post baseline TB available. Did gain some weight I would not call that a survivor)
007 – Not a responder, normal baseline TB, was AST/ALT responder, and not a weight responder, lack of post tx weight data. Did survive at least 7 years, but no survival data at end of study, lost to f/u
012 – Responder (*responder in AST in narrative data only, not in data sets, normal baseline TB, also responder in steatorrhea)
020– Responder (*responder in AST/ALT in T2, normal baseline TB)
021 – Responder (*in T2, normal baseline TB) Asklepion does not have this as a responder
032 - Not a responder only treated 2 years then lost to f/u, no documentation of survival. Is a responder in weight, AST/ALT and TB. Responder in steatorrhea, However, our criteria require two labs and survival and this pt does not have documented survival.
035 – Not a responder, responder in ALT. No baseline TB. only treated 6 months then lost to f/u. No documentation of survival
051 - ? pt started tx at age 10 had normal baseline ALT/TB, it is not clear that she benefited from tx did have baseline AST of 68 that made her technically a responder on wt, survival and AST
064 – Responder (*responder on histopathology)
046 – Responder (*in T2)
092 – Responder (*in T2)
703 – Responder (baseline and start of tx dates unclear, but close)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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ANISSA A DAVIS
03/11/2015

**From:** Dimick, Lara L
**To:** "Kellie Kennon" (kellie.kennon@asklepionpharm.com); Gary Pasternack (gary.pasternack@asklepionpharm.com)
**Cc:** Strongin, Brian K
**Subject:** FW: CHOLIC ACID-Structure of Adverse Reaction Section for Label
**Date:** Friday, March 06, 2015 12:02:05 PM

See also the changes below

*Lara*
*Lara Dimick-Santos, MD*
*Medical Team Leader*
*Liver and Inborn Errors of Metabolism Team*
*FDA/CDER/OND/ODE3/DGIEP*
*White Oak - Building 22, Room 5327*
*O - 301-796-4843*
*M - (b) (6)*
*Lara.Dimick@fda.hhs.gov*

**From:** Dimick, Lara L
**Sent:** Friday, March 06, 2015 11:40 AM
**To:** Kellie Kennon; Strongin, Brian K; Meyer, Joette M
**Cc:** Gary Pasternack; Beitz, Julie G; Murray, Jeffrey S; Gao, Wen-Yi
**Subject:** RE: CHOLIC ACID-Structure of Adverse Reaction Section for Label

This looks OK to me, but I would probably eliminate the repletion as highlighted.

## 6 ADVERSE REACTIONS

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical safety experience with CHOLBAM consists of:

- Trial 1: a non-randomized, open-label, (b) (4) trial of 50 patients with bile acid synthesis disorders due to SEDs and 29 patients with PDs including Zellweger spectrum disorders. Safety data are available over the 18 years of the trial.
- Trial 2: an extension trial of 12 new patients (10 SED and 2 PD) along with 31 (21 SED and 10 PD) patients who rolled-over from Trial 1. Safety data are available for 3 years and 11 months of treatment.

Adverse events were not collected systematically in either of these trials. Most patients received an oral dose of 10 to 15 mg/kg/day of CHOLBAM.

Deaths

In Trial 1, among the 50 patients with SEDs, 5 patients aged 1 year or less died, which included three patients originally diagnosed with AKR1D1 deficiency, one with 3b-HSD deficiency and one with CYP7A1 deficiency. The cause of death was attributed to progression of underlying liver disease in every patient.

Of the 29 patients in Trial 1 with PDs including Zellweger spectrum disorders, 12 patients between the ages of 7 months and 2.5 years died. In the majority of these patients (8/12), the cause of death was attributed to progression of underlying liver disease or to a worsening of their primary illness. Two additional patients in Trial 1 (1 SED and 1 PD) died who had been off study medication for more than one year with the cause of death most likely being a progression of their underlying liver disease. Of the patients who died with disease progression, laboratory testing showed abnormal serum transaminases, bilirubin, or cholestasis on liver biopsy suggesting worsening of their underlying cholestasis.

In Trial 2, among the 31 patients with SED, two patients (1 new patient and 1 who rolled over from Trial 1) died. The cause of death in both cases was unrelated to their primary treatment or progression of their underlying liver disease.

Of the 12 patients with PD in Trial 2, four patients died between the ages of 4 and 8 years (1 new patient and 3 who rolled over from Trial 1). The cause of death in three of these patients was attributed to progression of underlying liver disease or to a worsening of their primary illness.

Worsening Liver Impairment

Seven patients in Trial 1(4 SED and 3 PD) and 3 patients in Trial 2 (1 SED and 2 PD) experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy during treatment.

Common Adverse Reactions

There were 12 adverse reactions reported across 9 patients in the trials with diarrhea being the most common reaction in approximately 2% of the patient population. All other adverse reactions represented 1% of the patient population; (b) (4)

The breakdown (b) (4) by trial follows:

| Adverse Reactions | Trial 1 (b) (4) | Trial 2 (b) (4) * | Overall (b) (4) (%) |
|---|---|---|---|
| Diarrhea | 1 | 2* | 3 (2%) |
| Reflux Esophagitis | 1 | 0 | 1 (1%) |
| Malaise | 1 | 0 | 1 (1%) |
| Jaundice | 1 | 0 | 1 (1%) |
| Skin lesion | 1 | 0 | 1 (1%) |
| Nausea | 0 | 1* | 1 (1%) |
| Abdominal Pain | 0 | 1* | 1 (1%) |
| Intestinal Polyp | 0 | 1* | 1 (1%) |
| Urinary Tract Infection | 0 | 1* | 1 (1%) |
| Peripheral Neuropathy | 0 | 1 | 1 (1%) |

*Adverse reactions that occurred in new patients

Only one of the reactions (peripheral neuropathy) resulted in discontinuation of medication for a patient in Trial 2. An additional five SED patients (3 from Trial 1 and 2 from Trial 2) and 1 PD patient (Trial 1) discontinued medication and withdrew from the study due to a worsening of their primary disease.

The development of symptomatic cholelithiasis requiring cholecystectomy has been reported in a single patient with 3β-HSD deficiency.

*Lara*
*Lara Dimick-Santos, MD*
*Medical Team Leader*
*Liver and Inborn Errors of Metabolism Team*
*FDA/CDER/OND/ODE3/DGIEP*
*White Oak - Building 22, Room 5327*
*O - 301-796-4843*
*M - (b) (6)*
*Lara.Dimick@fda.hhs.gov*

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**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Friday, March 06, 2015 11:21 AM
**To:** Dimick, Lara L; Strongin, Brian K
**Cc:** Gary Pasternack
**Subject:** CHOLIC ACID-Structure of Adverse Reaction Section for Label

Good morning Lara Brian,

Per our discussion yesterday, I would welcome your thoughts on adverse event section below and whether you feel the way the data has been captured for the two trials will be sufficient. I understand that your feedback does not necessarily constitute a substantive review of content, but on the overall structure and format of the section.

Thank you in advance for your time.

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical safety experience with CHOLBAM consists of:

- Trial 1: a non-randomized, open-label, (b) (4) trial of 50 patients with bile acid synthesis disorders due to SEDs and 29 patients with PDs including Zellweger spectrum disorders. Safety data are available over the 18 years of the trial.
- Trial 2: an extension trial of 12 new patients (10 SED and 2 PD) along with 31 (21 SED and 10 PD) patients who rolled-over from Trial 1. Safety data are available for 3 years and 11 months of treatment.

Adverse events were not collected systematically in either of these trials. Most patients received an oral dose of 10 to 15 mg/kg/day of CHOLBAM.

Deaths

In Trial 1, among the 50 patients with SEDs, 5 patients aged 1 year or less died, which included three patients originally diagnosed with AKR1D1 deficiency, one with 3b-HSD deficiency and one with

CYP7A1 deficiency. The cause of death was attributed to progression of underlying liver disease in every patient.

Of the 29 patients in Trial 1 with PDs including Zellweger spectrum disorders, 12 patients between the ages of 7 months and 2.5 years died. In the majority of these patients (8/12), the cause of death was attributed to progression of underlying liver disease or to a worsening of their primary illness. Two additional patients in Trial 1 (1 SED and 1 PD) died who had been off study medication for more than one year with the cause of death most likely being a progression of their underlying liver disease. Of the patients who died with disease progression, laboratory testing showed abnormal serum transaminases, bilirubin, or cholestasis on liver biopsy suggesting worsening of their underlying cholestasis.

In Trial 2, among the 31 patients with SED, two patients (1 new patient and 1 who rolled over from Trial 1) died. The cause of death in both cases was unrelated to their primary treatment or progression of their underlying liver disease.

Of the 12 patients with PD in Trial 2, four patients died between the ages of 4 and 8 years (1 new patient and 3 who rolled over from Trial 1). The cause of death in three of these patients was attributed to progression of underlying liver disease or to a worsening of their primary illness.

Worsening Liver Impairment

Seven patients in Trial 1(4 SED and 3 PD) and 3 patients in Trial 2 (1 SED and 2 PD) experienced worsening serum transaminases, elevated bilirubin values, or worsening cholestasis on liver biopsy during treatment.

Common Adverse Reactions

There were 12 adverse reactions reported across 9 patients in the trials with diarrhea being the most common reaction in approximately 2% of the patient population. All other adverse reactions represented 1% of the patient population (b) (4)

The breakdown (b) (4) by trial follows:

| | Trial 1 (b) (4) | Trial 2 (b) (4) * | Overall (b) (4) (%) |
|---|---|---|---|
| Diarrhea | 1 | 2* | 3 (2%) |
| Reflux Esophagitis | 1 | 0 | 1 (1%) |
| Malaise | 1 | 0 | 1 (1%) |
| Jaundice | 1 | 0 | 1 (1%) |
| Skin lesion | 1 | 0 | 1 (1%) |
| Nausea | 0 | 1* | 1 (1%) |
| Abdominal Pain | 0 | 1* | 1 (1%) |
| Intestinal Polyp | 0 | 1* | 1 (1%) |
| Urinary Tract Infection | 0 | 1* | 1 (1%) |
| Peripheral Neuropathy | 0 | 1 | 1 (1%) |

*Adverse reactions that occurred in new patients

Only one of the reactions (peripheral neuropathy) resulted in discontinuation of medication for a patient in Trial 2. An additional five SED patients (3 from Trial 1 and 2 from Trial 2) and 1 PD patient (Trial 1) discontinued medication and withdrew from the study due to a worsening of their primary disease.

The development of symptomatic cholelithiasis requiring cholecystectomy has been reported in a single patient with 3β-HSD deficiency.

Thank-you

Kellie

Kellie A. Kennon, BSN | Senior Director of Clinical Research |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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/s/

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BRIAN K STRONGIN
03/06/2015

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** FW: Latest FDA Mark-Up of the CHOLBAM Labeling
**Date:** Wednesday, March 04, 2015 11:04:27 AM

---

Please note the comments and information requests below. Please ignore the previous version of this e-mail.

1. In order for us to verify the percent of patients with liver impairment before treatment, please confirm that the criteria remain the same as in the draft label of 12/15/2014, namely:

- Baseline liver dysfunction was determined by the following criteria: (1) ALT or AST values > 50 U/L; (2) total bilirubin values > 1 mg/dL, or direct bilirubin values > 0.3 mg/dL; (3) high levels of atypical urinary bile acids; and (4) evidence of cholestasis on liver biopsy. A total of xx/50 or xx% of patients met at least two of these criteria.

2. Please clarify whether these criteria have changed as our figures do not match the figures presented in this latest version of the label.

3. Should we continue to utilize the "at least two of the stated criteria?"

4. Is it possible for the Agency to send us the list of patients FDA feels meet this criteria to let us complete a reconciliation in advance of our upcoming call?

*We agree with the baseline criteria as listed above, but you need to specify the cut off level of atypical urinary bile acids at ≥ 2 to be considered "high".*

*See attached table of baseline hepatic dysfunction tables.*

Section 6: Adverse Reactions

1. The following statement was revised in the latest version received: "Trial 2: an extension trial of (b) (4) new patients ( (b) (4) SED and 2 PD)…. I believe the FDA reviewer corrected the figure from (b) (4) to (b) (4) new patients, but this includes subject 710 who was treated on an emergent basis, but discovered after study entry to have a diagnosis inconsistent with SED or PD and should not have been entered into the study. Although we understand the need to include for safety purposes, should we correct their designation from SED to "unknown"?

2. In the current version of the label, the (n=) has been changed (b) (4) for SED and (b) (4) to PD patients. The latest figures (b) (4) accounts for the discrepancy between the FDA figures and Asklepion's figures.

   We believe that (b) (4) Please confirm that patients who participated in both trials should be counted only once in Section 6 as well as in Section 5.1.

3. Deaths: The reviewer corrected the number of patient deaths (b) (4) SEC and (b) (4) PD, but left the subsequent sentence in: "Two additional patients (1 SED and 1 PD) died who had been off study medication for more than one year…" Please confirm whether the total count should remain the same or whether we can revert back to 7 and 16 with the clarifying sentence.

4. The reviewer commented that there were several patients who discontinued the study due to AE. Please confirm these should be listed, even if the events were not considered related to study drug.

*#1 -2 For Safety,(section 5.1 and 6) we have the total number of unique evaluable patients (Trials 1 and 2) is: SEDs = 50 + 5 and PD = 29 + 1.*
*#3 You may revert back to (b) (4) for the deaths and include the sentence about" the two additional patients……"*
*#4 You may delete references to the patients discontinued due to AE even if not thought to be drug related. If the AE events were liver related and or otherwise potentially related they should be listed.*

Section 14: Clinical Studies

1. In this latest revision, the FDA reviewer indicated that the (n=) for SED should be changed to 50, which would be reflective of the Responder ITT analysis. In the email exchange with FDA on 9Feb2015 and 10Feb2015, the Agency specified use of the mITT population (see Table 2 below). Does the Agency now wish to use the ITT population rather than the mITT? Reversion to the ITT (n=50), would include patients without enough data to conduct an analysis using the responder criteria.

   The confusion may lie in the fact that the definition of mITT for the responder analysis differs from the use of mITT in the 91-10-10 CSR. To be included in the earlier mITT analysis definition, a patient had to have enough data to perform an analysis on only a singer parameter (i.e. LFT, FAB, weight). The more stringent "responder analysis" required sufficient data in at least two parameters to qualify for the responder mITT. When the primary analysis was revised to the responder analysis, a review of patient data revealed that only 41 SED patients had enough data to be evaluated using the responder criteria.

2. Please confirm that the Agency intends for the responder analysis mITT population to be used for Table 2 in the label, below.

   *We agree with using the mITT population as you have defined it above. We also agree that it is confusing to list the two trials responders separately (b) (4) You should combine the data from trial 1 and 2 and count patients who crossed over into the extension trial only one time.*

3. New patients in CAC-002-01: The responder analysis provided as part of SN50 and included in Table 1 below, does include several treatment naïve patients where data was captured from CRFs that were not available at the time of the Day 120 safety update, and thus not included in any previously submitted datasets. The only treatment naïve patients where

data is available and presented in a dataset (or included as part of the Day 120 Safety Update) are: Patients 176, 700, 703, 705, 706 and 707. The status of the other patients follows in Table 1 below.

Please confirm whether the (n=) should be changed to only include the 6 patients where data is available and included in previously submitted dataset. More recent datasets are not available to support the analysis, unless the agency would consider paper CRFs as source.

*No we do not agree that you should include the patients for which you do not have data sets available to support the analysis. You should only include the six patients you have data for as noted above.*

*The only data sets we have from CAC-002-01 is height and weight, we have data listing but not electronic data sets for total bilirubin, AST/ALT or other indicators. Please provide complete data sets for CAC-002-01.*

Table 1

| | |
|---|---|
| Patient 701 | Only baseline data available per the dataset.<br>Used CRF data available and this patient was a "non-responder" as submitted. |
| Patient 702 | No data available to assess. Considered "non-evaluable" and not submitted as part of the recent responder analysis |
| Patient 704 | Only baseline data available per the dataset/CRF<br>Considered "non-evaluable" and not submitted as part of the recent responder analysis |
| Patient 708 | No baseline data available per the dataset/CRF<br>Considered "non-evaluable" and not submitted as part of the recent responder analysis |
| Patient 709 | Only a single set of labs available per dataset.<br>Used CRF data available and this patient was a "responder" as submitted. |
| Patient 710 | This patient was enrolled on an emergent basis and discovered following study entry to not have a SED or PD defect.<br>Considered "non-evaluable." |
| Patient 711 | No data available per dataset.<br>Used CRF data available and this patient was a "responder" as submitted. |
| Patient 712 | Only baseline data available per the dataset/CRF<br>Considered "non-evaluable" and not submitted as part of the recent responder analysis |
| Patient 713 | No data available per dataset.<br>Used CRF data available and this patient was a "responder" as submitted. |

Table 2

**91-10-10 Responder Analysis**

| **Single Enzyme Defects** | **mITT** | **ITT** |
|---|---|---|
| | # of Responders (24)/# Treated (41) | # of Responders (24)/# Treated (50) |
| 3b-HSD | 18/33 | 18/35 |
| AKR1D1 | 3/4 | 3/9 |
| CTX | 2/3 | 2/3 |
| AMACR | 1/1 | 1/1 |
| CYP7A1 | N/A | 0/1 |
| Smith-Lemli-Opitz | N/A | 0/1 |
| **Overall Responder Rate** | **58.5%** | **48%** |

| **Peroxisomal Disorders** | **mITT** | **ITT** |
|---|---|---|
| | # of Responders (11)/# Treated (26) | # of Responders (11)/# Treated (29) |
| **Overall Responder Rate** | **42%** | **38%** |

**CAC-002-01 Responder Analysis**

| **SED** | **mITT** | **ITT** |
|---|---|---|
| | # of Responders (27)/# Treated (29) | # of Responders (27)/# Treated (33) |
| 3b-HSD | 22/23 | 22/24 |
| AKR1D1 | 2/3 | 2/4 |
| CTX | 3/3 | 3/5 |
| **Overall Responder Rate** | **93%** | **82%** |

| **Peroxisomal Disorders** | **mITT** | **ITT** |
|---|---|---|
| | # of Responders (6)/# Treated (9) | # of Responders (6)/# Treated (12) |
| **Overall Responder Rate** | **67%** | **50%** |

As noted above after more internal discussion we fell that presenting the data for each trial is confusing (b) (4).

Therefore excluding the patients in table 1 who were initially included in the analysis I have:

SED total evaluable pts as 41 from 91-01-01 and 5 new patients in 002-01
SED responders 24 from 91-01-01, and all 5 of the new patients in 002-01 were responders (176, 700, 705 706, 707), as well as 3 more patients (027, 138, and 177) who were rolled over from trial 1 and became responders in trial 2 for a total of 32 of 46 patients

PD total evaluable is 26 from 91-01-01 and 1 more from 002-02-01
PD responders are 11 from 91-01-01 and 3 more rolled over who became responders (021, 046, 092) and one from 002-01 (703) for a total of 15 of 27 PD responders.

Do you agree with these numbers?

Thanks

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/s/

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BRIAN K STRONGIN
03/04/2015

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** PMR/PMC Schedule Commitment
**Date:** Tuesday, March 03, 2015 10:45:40 AM

---

Please propose definite dates for study completion and final report submission for the following PMR:

**A post-marketing prospective, long-term, observational study in a routine clinical setting of patients (b) (4) with bile acid synthesis disorders due to single enzyme defects and patients with peroxisomal disorders including Zellweger spectrum disorders who exhibit manifestations of liver disease. The purpose of the study is to assess primarily the long term safety of treatment with cholic acid. (b) (4) Additional evaluations will include dosing regimens and reasons for any dose modifications, weight gain, length/height and developmental outcomes. Specify concise case definitions and validation algorithms for all outcomes. Enroll at least 55 patients (25 receiving cholic acid and 30 not receiving cholic acid) including at least 20 peroxisomal disorder patients, with liver dysfunction, e.g. steatorrhea (b) (4) fat soluble vitamin deficiency or neuropathic process related to the latter. Enroll over an initial 3-year period and follow for a minimum of 10 years from the time of enrollment. (b) (4)**

**The timetable you submitted on February 20, 2015, states that you will conduct this study according to the following schedule:**

**Final Protocol Submission: September 2015**
**Study Completion: MM/YY**
**Final Report Submission: MM/YY**

Thanks

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BRIAN K STRONGIN
03/03/2015

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | Request for CHOLBAM NDA |
| **Date:** | Tuesday, March 03, 2015 4:59:04 PM |

Please respond to this comment ASAP.

**When you submit the datasets for CAC-002-01 (Trial 2), the patient ID numbers (i.e., PID) for those patients rolling over from Trial 1 need to be THE SAME as in Trial 1's datasets.**

**Hence if a patient participating in Trial 1 whose Trial 1 PID is, for example, 100, then when that patient rolls over into Trial 2 the PID should remain as 100 within Trial 2's datasets. Please make sure that this is the case.**

Thanks.

-

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BRIAN K STRONGIN
03/03/2015

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** FW: cholic acid
**Date:** Sunday, March 01, 2015 5:27:07 PM

---

Please respond to these information requests ASAP. Thanks.

1. With respect to the January 7, 2015 submission, with a cut-off date of September 30, 2012, there appears to be little or no information with which to assess response in treatment naïve patients beyond ID # 706. If Asklepion wishes to report responses in labeling for patients enrolled more recently (e.g., up through patient ID 713), please provide supporting documentation for these patients.

2. Asklepion and FDA appear to differ on the number of evaluable SED and PD patients as reported in the February 2015 listings for Study 91-10-10. There are only 41 SED patients in the mITT analysis rather than 50. We note responses in 3 of the 9 patients that were omitted (patients 078, 105, 134). Do you agree these patients are not evaluable for response? Likewise, please explain why there are only 26 evaluable PD patients rather than 29.

3. For the presentation of Trial 2 responses in labeling sections 14.1 and 14.2, Tables 3 and 4, please separate out the responses in continued patients and in treatment naïve patients, and present as two sub-columns within the Trial 2 column.

4. Submit all electronic datasets utilized to support the analyses and results presented within the CAC-002-01 CSR previously submitted on January 7, 2015.

Thanks.

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BRIAN K STRONGIN
03/01/2015

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | NDA 205750 CHOLBAM |
| **Date:** | Tuesday, February 24, 2015 10:26:35 AM |

Please submit a commitment to the following post-marketing commitment:

Develop a quantitative urinary bile acid analysis assay method along with standards for bile acid synthesis disorders.

Please provide a milestone date for final study report completion.

Thanks

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BRIAN K STRONGIN
02/24/2015

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** FW: NDA 205750 for CHOLBAM (cholic acid)
**Date:** Tuesday, February 24, 2015 3:20:03 PM
**Attachments:** MAPP Table Template.xls

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Please complete the attached tables, e-mail them to me and submit them to your NDA ASAP. Obtaining this information is very important and a delay will impact our action date. Thanks.

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BRIAN K STRONGIN
02/24/2015

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** sFW: was my cholic acid email re PMR comprehensible? i wasnt sure
**Date:** Monday, February 16, 2015 4:07:02 PM

---

Please submit a commitment to commit to perform the following PMR study:

A post-marketing prospective, long-term, observational study in a routine clinical setting of patients (b) (4) with bile acid synthesis disorders due to single enzyme defects and patients with peroxisomal disorders including Zellweger spectrum disorders who exhibit manifestations of liver disease. The purpose of the study is to assess primarily the long term safety of treatment with cholic acid. (b) (4) Additional evaluations will include dosing regimens and reasons for any dose modifications, weight gain, length/height and developmental outcomes. Specify concise case definitions and validation algorithms for all outcomes. Enroll at least 55 patients (25 receiving cholic acid and 30 not receiving cholic acid) including at least 20 peroxisomal disorder patients, with liver dysfunction, e.g. steatorrhea (b) (4) fat soluble vitamin deficiency or neuropathic process related to the latter. Enroll over an initial 3-year period and follow for a minimum of 10 years from the time of enrollment. (b) (4)

Final Protocol Submission: Asklepion to propose

Study Completion: Asklepion to propose

Final Report Submission: Asklepion to propose

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BRIAN K STRONGIN
02/16/2015

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | CHOLBAM Package Insert FDA Mark-Up and FDA Clean Copy |
| **Date:** | Wednesday, February 11, 2015 12:43:25 PM |
| **Attachments:** | CHOLBAM PI FDA Clean 11Feb2015.doc<br>CHOLBAM PI FDA Mark-Up 11Feb2015.doc |

I've attached a marked-up and clean copy (all changes accepted, comments left in) of the package insert so that you can make further changes. Please send me your marked-up version as soon as you can. Let me know If you have any questions.

24 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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BRIAN K STRONGIN
02/11/2015

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K; Dim, Cing D (NIH)
**Subject:** CHOLBAM (cholic acid) Clinical Information Request
**Date:** Monday, February 02, 2015 4:34:03 PM

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Please respond to this information request ASAP. Thanks.

Please provide narratives for the deaths and any Serious Adverse Events in the extension trial CAC-002-01.

Thanks.

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BRIAN K STRONGIN
02/02/2015

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | CHOLBAM: FDA Mark-Up of Sponsor Proposed Labeling |
| **Date:** | Tuesday, January 27, 2015 4:42:38 PM |
| **Attachments:** | CHOLBAM PI FDA Mark-Up Clean 1-27-15.doc<br>CHOLBAM PI FDA Mark-Up Underline - Strikeout 1-27-15.doc |

I've attached a clean and underlined/strikeout versions of the FDA mark-up of the proposed labeling that you submitted 1/13/15. Please add your changes in underlined/strikeout to the clean version and return to us ASAP. Thanks and let me know if you have any questions.

27 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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BRIAN K STRONGIN
01/27/2015

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** FW: IR for CHOLBAM (cholic acid)
**Date:** Wednesday, January 21, 2015 4:33:07 PM

---

Please respond to the information request below ASAP. Thanks.

1. Perform an analysis with the responder criteria as described below.

Response to CHOLBAM treatment was assessed by the following laboratory criteria: (1) ALT or AST values reduced to <less than 50 U/L, or baseline levels reduced by 80%; (2) total bilirubin values reduced to ≤ less than or equal to 1 mg/dL; (3) normalization of prothrombin time; and (34) no evidence of cholestasis on post-treatment liver biopsy, and the following clinical criteria: (1) body weight increased by 10% or stable at greater than the 50th percentile; and (2) alive at the last follow-up.

CHOLBAM responders were defined patients who either:

(1) met at least two of the laboratory criteria (above) and were alive at the last follow-up; or

(2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up.

Provide tables by type (SED and PD) and with the totals from the CAC 019-10-10 study in one table and second table with the results when the data from the CAC 002 study is used to assess response in the carryover patients and the results for the new patients (combined data). The table columns should have pt ID, baseline ALT/AST, ALT/ALT <50 or reduced by 80%, baseline total bili, total bili reduced to < 1, baseline PT/INR, Normal Prothrombin time/INR (response), no cholestasis on liver biopsy, body weight > 10%, or stable at > 50$^{th}$ percentile, alive at last follow-up, and the last column should contain the responder definition (i.e.,1- met at least two of the laboratory criteria (above) and were alive at the last follow-up; or 2 - met at least one laboratory criterion, had increased body weight and were alive at the last follow-up)

2. Provide data to support your claim in the labeling:

(b) (4)

Thanks

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BRIAN K STRONGIN
01/21/2015

# MEMORANDUM OF TELECONFERENCE

**Teleconference Date**: December 15, 2014

**Application Number**: NDA 205750
**Product Name:** CHOLBAM (cholic acid) Capsules
**Sponsor/Applicant Name:** Asklepion Pharmaceuticals, LLC

**Subject**: Paroxisomal Disease (PD) Patients, Registry Study, (b) (4) Labeling, Bioequivalence Studies, and Rare Pediatric Disease Priority Review Voucher

**FDA Participants**

| | |
|---|---|
| Julie Beitz, M.D. | Director, Office of Drug Evaluation III |
| Donna Griebel, M.D. | Director, Division of Gastroenterology and Inborn Errors Products (DGIEP) |
| Lara Dimick, M.D. | Medical Team Leader DGIEP |
| Wen-Yi Gao, M.D. | Medical Officer, DGIEP |
| Sue-Chih Lee, Ph.D. | Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP III) |
| Insook Kim, Ph.D. | Clinical Pharmacology Reviewer, DCP III |
| Ben Vali, M.S. | Statistical Reviewer, Office of Biometrics III |
| Ethan Hausman, M.D. | Medical Officer, Pediatric and Maternal Health Staff |
| David Joseph, Ph.D. | Pharmacology/Toxicology Team Leader, DGIEP |
| Ke Zhang, Ph.D. | Pharmacology/Toxicology Reviewer, DGIEP |
| Carolyn McCloskey, M.D. | Medical Officer, Division of Epidemiology III |
| Denise Pica-Branco, Ph.D. | Senior Regulatory Health Project Manager |
| Brian Strongin, R.Ph., MBA | Chief, Project Management Staff |

**Sponsor/Applicant Participants**

| Name | Affiliation |
|---|---|
| Gary Pasternack, MD, PhD | CEO, Asklepion |
| Jeff Courtney | COO, Asklepion |
| Kellie Kennon, BSN | Director, Clinical Research, Asklepion |
| Gemma Hodgson, BS | Clinical Research Associate, Asklepion |
| (b) (4) | Consultant |
| (b) (4) | Consultant, (b) (4) |

**BACKGROUND**:

NDA 205750 was submitted November 21, 2013 for CHOLBAM (cholic acid) Capsules.

Proposed Indication: [redacted] (b) (4)

PDUFA Goal Date: October 21, 2014

**DISCUSSION**:

Paroxisomal Disease Patients

The Division opened by stating that the FDA mark-up of the sponsor's proposed labeling had recently been e-mailed to Asklepion and that the labeling included patients that improved as well as those that worsened since it had been difficult to devise responder criteria.

PMR Registry Study

The Division reminded the sponsor that a template for the PMR registry study had been sent to them recently. The study should include both PD patients and patients with Single Enzyme Defects and it should explore the effects of different doses. The Division asked the sponsor to submit their proposal for the registry study as soon as possible. The sponsor asked if they could submit a synopsis rather than a complete draft protocol. They explained that they could submit a synopsis quickly. The Division responded that a synopsis was acceptable and that it should include submission milestone dates. The protocol could be fleshed out after an Approval action. The Division commented that the registry study would last for several years and that the Division would need annual updates on the progress of the study.

[redacted] (b) (4) Labeling

The Division and the sponsor agreed that the sponsor would [redacted] (b) (4) include [redacted] (b) (4) package insert labeling. [redacted] (b) (4)

Bioequivalence Studies

The Division commented that the bioequivalence study comparing the clinical trials formulation to the to-be-marketed formulation did not show bioequivalence. These data are still under review. A post-marketing requirement may be needed or the bioequivalence study may be subsumed into the registry study.

Rare Pediatric Disease Priority Review Voucher

The sponsor reminded the Division that they had submitted an application for a Rare Pediatric Disease Priority Review Voucher. The Agency is reviewing the application.

FDA Mark-up of the Sponsor's Proposed Labeling

The sponsor stated that they had no major issues with the FDA mark-up and that they would respond to it soon.

**ACTION ITEMS:**

- The sponsor will submit a synopsis of their proposal for the registry study as soon as possible.
- The sponsor will [redacted] (b) (4) include [redacted] (b) (4) package insert labeling.
- The Division will complete their review of the bioequivalence studies.
- The Agency is reviewing the sponsor's application for a Rare Pediatric Disease Priority Review Voucher.
- The sponsor will respond to the FDA mark-up of their proposed labeling soon.

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/s/

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BRIAN K STRONGIN
01/02/2015

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K; Dimick, Lara L; Beitz, Julie G |
| **Subject:** | Information Request for NDA 205750 CHOLBAM (cholic acid NDA) |
| **Date:** | Wednesday, December 31, 2014 11:04:00 AM |

Please respond to this information request ASAP:

Please discuss the treatment of cerebrotendinous xanthomatosis (CTX) with cholic acid vs. chenodeoxycholic acid. Specifically please discuss the differences in response in cholestanol levels, bile alcohols and clinical signs and symptoms to treatment with these two different bile acids.

Thanks

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BRIAN K STRONGIN
12/31/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | FW: CHOLBAM Information Request |
| **Date:** | Tuesday, December 23, 2014 12:49:38 PM |

We are interested in seeing whether patients who switched from the pharmacy formulation to the TBM formulation remained stable in their response to treatment. We have detailed info on the impact of the switch in 16 patients at 30 days post switch. These 16 patients then rolled into CAC-002-01, along with perhaps several others. We would like to see If the interim CSR (due Jan 6) will provide info on the impact of the switch on efficacy beyond 30 days. Thanks.

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Monday, December 22, 2014 2:21 PM
**To:** Strongin, Brian K; kellie.kennon@asklepionpharm.com
**Subject:** RE: CHOLBAM Information Request

Brian,

Regarding the Agency's request for the CSR for "CAC-002-01 -An Open-Label, Single-Center, Non-Randomized Continuation Study of Cholic Acid Capsules in Subjects with Inborn Errors of Bile Acid Synthesis" we are preparing the following response and would like the Agency's confirmation that the planned response is acceptable.

CAC-002-01 presently remains an open study because it serves as a vehicle to continue to provide cholic acid to patients previously enrolled in Study 91-10-10, and to patients identified since the closure of 91-10-10. By prior agreement with the Agency, safety data were included in the Day 120 ISS safety update, submitted as SN011. The cutoff date for the safety data included in the ISS was November 30, 2013. We have an interim CSR that we plan to upload early in the week of January 6, 2015. Our plan is to upload the CSR body and all appendices. The cutoff date for the interim CSR was September 30, 2012. We are unable to upload the CSR any sooner because the staff of our publishing vendor is off for the holidays.

Following approval, Asklepion plans to close out CAC-002-01 and to prepare a full CSR. Asklepion plans to submit a full CSR to the Agency during the fourth quarter of 2015.

Please let us know if this plan is acceptable to the Agency.

Sincerely,

Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**


729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



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**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
**Sent:** Friday, December 19, 2014 5:00 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** CHOLBAM Information Request

Please respond to this information request ASAP:

Please provide a study report or inform us where it is located in the submission for CAC-002-01 -An Open-Label, Single-Center, Non-Randomized Continuation Study of Cholic Acid Capsules in Subjects with Inborn Errors of Bile Acid Synthesis.

Thanks.

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/s/

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BRIAN K STRONGIN
12/23/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | CHOLBAM Information Request |
| **Date:** | Friday, December 19, 2014 5:00:24 PM |

Please respond to this information request ASAP:

Please provide a study report or inform us where it is located in the submission for CAC-002-01 -An Open-Label, Single-Center, Non-Randomized Continuation Study of Cholic Acid Capsules in Subjects with Inborn Errors of Bile Acid Synthesis.

Thanks.

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/s/

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BRIAN K STRONGIN
12/19/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Beitz, Julie G; Dimick, Lara L; Griebel, Donna; Strongin, Brian K |
| **Subject:** | RE: cholic acid NDA |
| **Date:** | Monday, December 15, 2014 10:51:29 AM |
| **Attachments:** | CHOLBAM Draft Package-Insert-Word FDA Mark-Up 12-15-14.doc |

I've attached a draft FDA mark-up of your latest proposed package insert. There may be further editing , but you can start reviewing and filling in the numbers that we have asked you to provide in sections 5.1, 14.1 and 14.2.

In addition, please respond to the information request below about the statement in Section 2.1 ASAP.

- Please provide a justification and rational for the statement in Section 2.1 of the labeling that a higher dose of CHOLBAM may be required in patients with familial hypertriglyceridemia. Provide the amount the dose may need to be increased and a justification for this amount.

Thanks,

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

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BRIAN K STRONGIN
12/15/2014

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K; Dimick, Lara L; Beitz, Julie G
**Subject:** FW: Cholic Acid Pregnancy Surveillance Program
**Date:** Thursday, December 11, 2014 10:00:16 AM
**Attachments:** Cholbam pregnancy surveillance program IR.doc

---

Please see the language about the addition of a pregnancy surveillance program to your product registry:

While there are case reports of pregnant women taking Cholbam in the published literature, there is insufficient evidence to clearly determine the effect of Cholbam on reproduction, labor or delivery, and lactation in patients with inborn errors of bile acid synthesis. Because these limited reports do not provide reassurance about the potential risks to the mother or fetus when Cholbam is used during pregnancy, we recommend that a pregnancy surveillance program be established within the postmarketing product registry. Data collection within the pregnancy surveillance program should align with the Agency's "Guidance for Industry: Establishing Pregnancy Exposure Registries", August 2002, Attachment B. You should submit your protocol or data collection sheets for obtaining pregnancy exposure data, which includes the suggested data elements described in the guidance.

A pregnancy surveillance program is another method of collecting meaningful pregnancy exposure data; especially when a prospective observational pregnancy cohort study is not feasible. Pregnancy surveillance programs can enroll prospective and retrospective cohorts. Demographic data, medical history, and pregnancy outcomes information is collected on enrollees. Many pregnancy exposure surveillance programs are set up to collect data similar to that collected in pregnancy exposure registries. Data is collected at various time points during a pregnancy and infants are generally followed for 12 months. Control groups are not required in pregnancy surveillance programs.

Thanks and let me know if you have any questions.

---

**From:** Dimick, Lara L
**Sent:** Wednesday, December 10, 2014 10:39 PM
**To:** Beitz, Julie G; Mulberg, Andrew
**Cc:** McCloskey, Carolyn A; Strongin, Brian K
**Subject:** FW: Cholic Acid Pregnancy Surveillance Program

These are excellent suggestions from Tamara for addition to the registry for pregnancy surveillance. I think we should send to the sponsor, but wanted to run by you before I did so.

*Lara*
*Lara Dimick-Santos, MD*

*Medical Team Leader*
*Liver and Inborn Errors of Metabolism Team*
*FDA/CDER/OND/ODE3/DGIEP*
*White Oak - Building 22, Room 5327*
*O - 301-796-4843*
*M - (b) (6)*
*Lara.Dimick@fda.hhs.gov*

---

**From:** Johnson, Tamara
**Sent:** Wednesday, December 10, 2014 6:04 PM
**To:** Dimick, Lara L
**Subject:** Cholic Acid Pregnancy Surveillance Program

Hello Lara,

As promised, attached is language that should help Asklepion understand what to do to. Please let me know if you have any further questions.

Tamara Johnson, MD, MS
Medical Officer
Division of Pediatric and Maternal Health

Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Bldg 22, Rm 6319
Silver Spring, MD 20993-0002
(301) 796-1522

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/s/

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BRIAN K STRONGIN
12/11/2014

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** FW: ONDQA Comments on (b) (4) for NDA 205750 CHOLBAM
**Date:** Wednesday, December 10, 2014 4:21:29 PM

Please respond to this information request ASAP.

Please make the following changes (b) (4)

(b) (4)

Thanks.

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/s/

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BRIAN K STRONGIN
12/10/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | Information Request for NDA 205750 Cholic Acid |
| **Date:** | Tuesday, December 09, 2014 2:30:57 PM |

Please respond to the following information request ASAP.

For the following patients: 012, 020, 021, 030, 032, 035, 046, 051, 092, 132, 173

- Please provide any data or information you have on the presence or absence of steatorrhea or diarrhea prior to cholic acid treatment and resolution or not of steatorrhea or diarrhea after treatment.

- Please provide any data or clinical information on presence of absence of coagulopathy prior to treatment and the response of coagulopathy to treatment.

Thanks.

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BRIAN K STRONGIN
12/09/2014

# MEMORANDUM OF TELECONFERENCE

**Teleconference Date**: November 18, 2014

**Application Number**: NDA 205750
**Product Name:** CHOLBAM (cholic acid) Capsules
**Sponsor/Applicant Name:** Asklepion Pharmaceuticals

**Subject**: Indications Statement, Dose Adjustments, Bile Acid Measurements by FAB MS, Post-Marketing Studies

**FDA Participants**

| | |
|---|---|
| Julie Beitz, M.D. | Director, Office of Drug Evaluation III |
| Joyce Korvick, M.D | Deputy Director for Safety, Division of Gastroenterology and Inborn Errors Products (DGIEP) |
| Lara Dimick, M.D. | Medical Team Leader, (DGIEP) |
| Wen-Yi Gao, M.D. | Medical Officer, DGIEP |
| Joette Meyer, Pharm.D. | Acting Associate Director for Labeling, DGIEP |
| Insook Kim, Ph.D. | Clinical Pharmacology Reviewer, Division of Clinical Pharmacology III |
| Ben Vali, MS | Statistician, Division of Biometrics III |
| Carolyn McCloskey, M.D., MPH | Epidemiology Reviewer, Division of Epidemiology II (DEPI II) |
| Sukhminder Sandhu, M.D. | Director Regulatory Affairs, DEPI II |
| David Shih, M.D. | Lead Medical Officer, DEPI II |
| Ethan Hausman, M.D. | Medical Officer, Division of Pediatric and Maternal Health (DPMH) |
| Denise Pica-Branco, Ph.D. | Senior Regulatory Health Project Manager, DPMH |
| Brian Strongin, R.Ph., MBA | Chief, Project Management Staff, DGIEP |

**Sponsor/Applicant Participants**

| Name | Affiliation |
|---|---|
| Gary Pasternack, MD, PhD | CEO, Asklepion |
| Jeff Courtney | COO, Asklepion |
| Kellie Kennon, BSN | Director, Clinical Research, Asklepion |
| Gemma Hodgson, BS | CRA, Asklepion |
| (b) (4) | Consultant |
| (b) (4) | Consultant, (b) (4) |
| (b) (4) | Consultant, (b) (4) |

**BACKGROUND**:

NDA 205750 for CHOLBAM (cholic acid) Capsules was submitted November 21, 2013 (b) (4) This teleconference concerned the following issues: the Indications statement, dose adjustment information and information about bile acid measurements by FAB-MS in the package insert and the need for a post-marketing study. The agenda is attached in Appendix A. The Proposed PMR Study Concept Outline is attached in Appendix B. Both documents were sent to Asklepion before the meeting.

**DISCUSSION**:

Indication Statement

The sponsor stated that they agreed with the Division's analysis of the data on patients with single enzyme defects (SEDs) (b) (4) The Division asked the sponsor to confirm the Division's analysis of SED patients as well as PD patients.

The discussion then turned to the following wording in the indications statement:

"CHOLBAM is indicated (b) (4) for the treatment of bile acid synthesis disorders involving single enzyme defects … ".

Asklepion stated that, they would submit literature supportive of their position that, although there is no standard of care, in addition to cholic acid, patients receive vitamins for symptomatic treatment of deficiencies.

The FDA agreed to delete the words (b) (4)

(b) (4)

The Division stated that (b) (4) data from the registry, to be requested as a post-marketing study, (b) (4) Other than a recommendation to stop CHOLBAM after three months of treatment if the patient is experiencing cholestasis and shows signs of liver damage, or no improvement on treatment, (b) (4) Division stated that they realized that the package insert may not match what happens in clinical practice.

Bile Acid Measurements by FAB-MS

The Division stated that information in the label about FAS-MS used for diagnosis could remain. (b) (4) The sponsor agreed to develop a better assay for analyzing urine bile acids along with standards for the other subtypes of SED patients.

Post-Marketing Study and Peroxisomal Disease

Asklepion stated that peroxisomal disease (PD) was a heterogeneous disease and that it is difficult to identify patients that may respond to CHOLBAM. They added that some PD patients responded well.

The discussion then turned to the need for a post-marketing efficacy and safety registry study enrolling patients treated with CHOLBAM for either single enzyme defects or peroxisomal disease. The Division stated that it realized that, although CHOLBAM might be effective for some patients, there isn't sufficient data to show efficacy. Asklepion was encouraged to gather more data in a registry study. Asklepion stated that they couldn't commit to a registry study at this time. They added that, if the PD indication was not approved, patients would bare an undue burden because CHOLBAM may not be covered by their health insurance. In addition, they added that Asklepion may not have sufficient resources to conduct another study. It was their goal to stop clinical trials when their NDA was approved. The Division responded that they received comments from Office of New Drugs upper management on the CHOLBAM application and there was consensus that data supporting the safety and efficacy of CHOLBAM for PD was lacking. In addition, there is evidence that CHOLBAM may be harmful to some PD patients.

Asklepion stated that they never claimed that CHOLBAM provided a survival benefit to PD patients. They believe that CHOLBAM is an adjunct in PD patients to prevent future liver disease.

The Division also recommended that Asklepion consider conducting a randomized withdrawal study in PD patients and include a rescue treatment. Patients may be less resistant to a study conducted under an IND since they would not have to pay for the CHOLBAM.

**ACTION ITEMS:**

Asklepion will confirm the Division's analysis of SED patients as well as PD patients.

Attachments:

Attachment A – Agenda
Attachment B – Proposed PMR Study Concept Outline

Attachment A – Agenda

**Discussion Topics for Teleconference with Asklepion on November 18, 2014**

**1. Indication Statement**

We refer to the wording of your proposed indication statement for Cholbam:

(b) (4)

We also refer to the minutes of a Type B meeting held on October 25, 2004 in which we stated:

> "The wording in the various sections of the labeling, including what specific enzyme defects may be treated with cholic acid is a review matter. For example, we would not anticipate approving the use of cholic acid for conditions that are clinically unresponsive to the bile acid…"

Based upon our review of the data submitted in your NDA and available data in the published literature, we propose the following wording for the indication statement for Cholbam:

"CHOLBAM is indicated (b) (4) for the treatment of bile acid synthesis disorders involving single enzyme defects, (b) (4)

(b) (4)

Our proposal is based on our preliminary assessment of response to Cholbam. Response was assessed by the following laboratory criteria: (1) ALT or AST values reduced to <50 U/L, or baseline levels reduced by 80%; (2) total bilirubin values reduced to ≤ 1 mg/dL; and (3) no evidence of cholestasis on liver biopsy, and the following clinical criteria: (1) body weight increased by 10% or stable at > 50$^{th}$ percentile; and (2) alive at the last follow-up.

Cholbam responders were defined as patients who either (1) met at least two of the laboratory criteria and were alive at the last follow-up; or (2) met at least one laboratory criterion, had increased body weight and were alive at the last follow-up. Overall, 31of the 50 patients responded as shown below.

**Table 1. Response to CHOLBAM Treatment by Type of Enzyme Defect**

| Single Enzyme Defect | Number of Responders/ Number Treated |
|---|---|
| 3β-HSD | 24/35 |
| AKR1D1 | 3/9 |
| CTX | 3/3 |

| | |
|---|---|
| AMACR | 1/1 |
| CYP7A1 | 0/1 |
| Smith-Lemli-Opitz | 0/1 |

**2. Cholbam** (b) (4)

Based upon our review of the data submitted in your NDA and available data in the published literature, we agree that patients should be monitored closely, especially during the initial months of Cholbam treatment, and that the lowest dose of Cholbam that effectively maintains hepatic function should be chosen.

We believe that evaluation of hepatic function, including measurement of transaminases, PT/INR, and serum bilirubin, and clinical parameters should be used for initiation of dosing, and decisions regarding continuation of dosing. (b) (4)

(b) (4)

**3. Bile acid measurements by FAB-MS**

In previous meetings (e.g., September 25, 2007; December 6, 2007; January 25, 2010) we were open to the idea of changes in "readily identifiable and measurable short-term endpoints", including reduction in atypical bile acids, as potential surrogates for clinical efficacy. However, in our minutes of the January 2010 meeting we also stated that "your proposal and description of the changes in FAB-MS is limited by its inability to provide quantification". We suggested instead that you consider using alternative methods, such as GC/LC-MS, to measure bile acids in urine and serum.

Based upon our review of the data submitted in your NDA and available data in the published literature, we believe that bile acid measurements by FAB-MS may be appropriate in the diagnosis of patients with bile acid synthesis disorders. (b) (4)

We encourage you to generate information regarding GC-MS or LC-MS to support their use in the clinical monitoring of patients on cholic acid, in accordance with the guidance provided in our January 2010 meeting (i.e., by providing adequate validation for the bioanalytical assay methods used, identifying specific atypical bile acids to assess for each SED type, and correlating the results of atypical bile acids with clinical outcomes).

## 4. Postmarketing Study

We intend to require a postmarketing efficacy and safety registry study to further assess clinical and laboratory outcomes in patients treated with cholic acid. We recommend that data be collected systematically on both patients with bile acid synthesis disorders involving single enzyme defects and patients with peroxisomal disorders. A template is attached to facilitate development of a draft protocol.

Appendix B – Proposed PMR Study Concept Outline

**Cholic Acid Proposed PMR Study Concept Outline**

| | |
|---|---|
| **Study Design** | • Describe the study design of a PMR study/registry. |
| **Study Objective (s)** | • State the primary and any secondary objectives of the study. You should evaluate potential safety outcomes of worsening or new hepatic dysfunction/cholestasis, failure to thrive, and death. You should also evaluate improvements in clinical outcomes such as growth and survival. You should also gather data to support dose adjustment. |
| **Data Sources** | • Describe the data sources you will use to address the study objectives. |
| **Study Population & Sample Size** | • Describe your cholic acid-exposed group(s) and any possible comparator group(s).<br>• Provide the minimum number of patients you expect to enroll in each group and how you calculated this number. |
| **Entry Criteria** | • Describe enrollment inclusion and exclusion criteria. You should include both patients with single enzyme defects and peroxisomal disorders. |
| **Follow-up** | • Describe the possible follow-up period and any patient censoring criteria.<br>• Describe plans to minimize missing data, especially for patients who are lost to follow-up.<br>• Describe recruitment plans, especially to offset the impact of patients lost to follow-up. |
| **Validation of Exposure/Outcome** | • Indicate whether you will validate and adjudicate exposures and outcomes, including worsening or new hepatic dysfunction/cholestasis (clinicial and laboratory), other outcomes related to liver disease such as coagulopathy, steatorrhea, hepatosplenomegaly.failure to thrive, growth, neurologic outcomes, and causes of death.<br>• Indicate how you will capture death outcomes (e.g., linkage to databases.) |
| **Covariates** | • Indicate the ability of the study to capture and adjust for potential confounders, including but not limited to: subtype of inborn error, age, sex, concomitant medications.<br>• |
| **Analysis Plan** | • Describe the hypothesis you will test in the primary analysis.<br>• Consider comparing height/length and weight changes in the cholic acid exposed groups against standardized height/length and weight trajectories of normal children.<br>• Describe the statistical methods used for the primary analysis and the ability to control for potential confounders (see Covariates above).<br>• Describe any sensitivity analyses you will conduct. |
| **Milestones and Reporting** | Propose dates for:<br>• Final Protocol Submission<br>• Interim Report(s) Submission<br>• Study Completion<br>• Final Report Submission |

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/s/

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BRIAN K STRONGIN
12/04/2014

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K; Beitz, Julie G; Dimick, Lara L
**Subject:** FW: Status of Reanalysis of PD Patient Data - DRAFT
**Date:** Thursday, December 04, 2014 4:51:10 PM

---

Regarding your e-mail below:

1. Please submit your analysis of single enzyme defect patients by the criteria described in the document, "Discussion Topics for Teleconference with Asklepion on November 18, 2014".
2. Describe the "slightly modified criteria" used to analyze patients 30 and 132.

Thanks.

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Wednesday, December 03, 2014 6:33 PM
**To:** Strongin, Brian K
**Cc:** 'Kellie Kennon'; Beitz, Julie G; Dimick, Lara L; (b) (4)
**Subject:** RE: Status of Reanalysis of PD Patient Data - DRAFT

Brian,

Sorry for the delay in not getting this to you earlier today. We have re-analyzed the patients using the criteria that were in the document, "Discussion Topics for Teleconference with Asklepion on November 18, 2014". We disagree with the statement that there were no responders among the peroxisomal biogenesis disorder patients. We would like to bring the following to your attention, but at the same time do not wish to trigger any undue delays at this point. We wish to ask the Agency's advice as to whether this re-analysis should be submitted formally. Please note that the bilirubin was problematic in terms of the criteria for PD patients. In most patients, it was never elevated and therefore it was impossible to demonstrate a reduction. Weight gain is also more problematic in PD patients since their failure to thrive is due to the non-hepatic systemic manifestations of their disorders as well as to the hepatic component; when weight gain occurs, it is meaningful, but most PD patients remain as failures to thrive. This is consistent with our view of cholic acid as adjunctive therapy to treat the hepatic component of peroxisomal biogenesis disorders. Including the responders by slightly modified criteria, we believe 5 of 29 patients show documented responses. We note three additional patients, 20, 21, and 51, who demonstrated stabilization but never met the FDA criteria, largely because their initial laboratory values were not particularly high, and/or because the post-treatment transaminase values were slightly above 50 U/L.

RESPONDERS BY FDA CRITERIA

Patient 32
The AST was reduced by 80% from pre-treatment peak to post treatment peak, and the bilirubin was reduced to less than 1 mg/DL. The patient was alive and well after last follow-up. The ALT also showed a reduction, but there was one excursion on treatment to 64 U/L

Patient 35
The ALT was reduced by 80% from the pre-treatment peak to the post-treatment value. The patient's weight increased by slightly over 10% from the last pre-treatment measurement to the last post-treatment measurement. The patient was alive and well at last follow-up. The AST also declined markedly, but not quite by 80%.

Patient 173
The ALT was reduced to less than 50 U/L, and the AST was reduced by 79% comparing pre-treatment peak to the post-treatment value. The patient's weight increased by greater than 10% in the first month following therapy. No post-treatment bilirubins were available. The patient was alive and well at last follow-up.

RESPONDERS BY MODIFIED CRITERIA AS NOTED

Patient 132
The ALT was reduced to less than 50 U/L and the AST was reduced by greater than 80% comparing peak pre-treatment values to peak post-treatment values. The bilirubin was stably under 1.0 mg/DL, which was considered a criterion for response. The patient was alive and well when the CAC-91-10-10 study terminated, but subsequently died following a pamidronate infusion.

Patient 30
The ALT and AST were both reduced by greater than 80% comparing peak pre-treatment values to peak post-treatment values, excluding a single significant elevation that occurred on June 6,1993 that subsequently returned to baseline. The bilirubin was reduced to less than 1.0 mg/DL. The patient was alive and well at the last visit.

Please let me know your thoughts as to anything else that might be required.

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

**that this email or any attachment to it is free of computer viruses or other conditions which may damage or interfere with data, hardware or software with which it might be used.**

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**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
**Sent:** Tuesday, December 2, 2014 5:17 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K; Beitz, Julie G; Dimick, Lara L
**Subject:** Status of Reanalysis of PD Patient Data

Please give me an update on the status of your reanalysis of the PD patient data. Thanks.

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/s/

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BRIAN K STRONGIN
12/04/2014

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** FW: NDA 205750
**Date:** Tuesday, October 14, 2014 3:29:11 PM

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We have the following response to your question below:

"When we conducted our review of the missing bilirubin data, we discovered that there are a total of 22 patients affected. 19 of the patients are in the 3HSD subgroup; 1 in CTX; 1 Peroxisomal and 1 delta. **We would like the agency to comment on whether it is necessary to conduct analyses on all of those subgroups or just in the 3HSD subgroup, since it is only that subgroup where any effect could be meaningful.** Our intention is to submit the revised analyses as well as the graphical presentation of the data in these patients."

*FDA Response: Please provide all the additional data and all the requested reanalysis for completeness.*

Thanks.

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Friday, October 10, 2014 11:21 AM
**To:** Strongin, Brian K
**Cc:** 'Kellie Kennon'
**Subject:** NDA 205750

Dear Brian,

Thank you for your emails regarding the outstanding clinical information requests. The following is a summary of what we are currently working on and answers to a few of your questions:

1. We have met with our statistical and clinical teams and are working toward a submission date of October 17, 2014 for the peroxisomal patient information requested. Cincinnati Children's Hospital Medical Center has provided us with substantial follow-up data on the long term survivors that we feel the review team will find most helpful. Our goal will be to provide responses to the questions posed in the September 30, 2014 Clinical IR as well as revised narratives for the long term survivors in the next submission.

2. The next submission(s) will include analyses (bilirubin, scatter plots) and responses to the agency's questions no later than October 31, 2014. We may be able to submit portions of this response earlier, but the 31$^{st}$ of October represents a date certain. The rate limiting steps are the capacity of our statistical team and the subsequent time required for QC and publishing. This submission would include the bilirubin analyses and revised narratives for the affected patients per the 30 Sep 2014 IR. There is an important point, however, to consider:

    a. When we conducted our review of the missing bilirubin data, we discovered that

there are a total of 22 patients affected. 19 of the patients are in the 3HSD subgroup; 1 in CTX; 1 Peroxisomal and 1 delta. We would like the agency to comment on whether it is necessary to conduct analyses on all of those subgroups or just in the 3HSD subgroup, since it is only that subgroup where any effect could be meaningful. Our intention is to submit the revised analyses as well as the graphical presentation of the data in these patients.

We continue to be grateful for the patience, time and collaboration that the agency has provided and will do everything possible to expedite the submissions and provide them earlier than the dates indicated above.

We continue to be grateful for the patience, time and collaboration that the agency has provided and will do everything possible to expedite the submissions.

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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/s/

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BRIAN K STRONGIN
10/14/2014

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|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | NDA 205-750 Cholic Acid Information Request |
| **Date:** | Thursday, October 09, 2014 10:59:51 AM |

Please respond to these information requests ASAP:

Give me an update on the status of your response to the 9/30/14 Clinical Information Request.

Verify whether the 15 patients described in the paper published by Gonzales et al. (Gastroenterology, 2009) are also included in the NDA. If they are, please provide the relevant patient ID numbers. If you have not already done so, please formally submit this paper to your NDA.

Thanks.

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/s/

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BRIAN K STRONGIN
10/09/2014

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** NDA 205-750 Cholic Acid Clinical Information Request
**Date:** Thursday, October 09, 2014 3:19:16 PM

---

One more clinical information request:

Please submit any data you have from the trial of cholic acid therapy in 20 mild Zellweger spectrum patients conducted in The Netherlands at Emma Pediatric Hospital, Amsterdam; Dr. Bart Koot is the PI.

Please respond ASAP. Thanks.

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/s/

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BRIAN K STRONGIN
10/09/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | Gary Pasternack; "Kellie Kennon" |
| **Cc:** | Strongin, Brian K |
| **Subject:** | RE: NDA 205-750 Cholic Acid Clinical Information Request |
| **Date:** | Tuesday, September 30, 2014 12:19:11 PM |

Here is the revised clinical information request. Please respond ASAP and let me know if you have any questions. Thanks.

1. **You used the term "cholestasis" in several different ways in the narratives referencing both urine and clinical abnormalities. Provide the definition(s) of the term "Cholestasis" as used in your narratives.**

2. **Provide the rationale for treating patients with Peroxisomal Disease (PD) and normal urinary bile acids at baseline. In your submission, some PD patients (PIDs 7, 11, 17, 19, 29, 30, 51, 64, and 92) had normal urinary bile acid at baseline. Some of these patients also had normal total bilirubin or near normal transaminases at baseline.**

3. **Provide the rationale for treating PD patients with normal bilirubin, or normal transaminases at baseline (e.g., patient 051).**

4. **Some of the patients with PD had reversible increases of transaminases shortly after bile acid therapy (PIDs 7, 11, 64, and 69) or non-reversible increase after the treatment (PID 21). Please explain the potential causes of the worsening in transaminases.**

5. **Forty-eight percent (14/29) of the patients in the PD population died at a young age. However, we note different outcomes with longer life span in some cases (PIDs 012, 020, 021, 046, and 092) and in some cases reports of "normal function". Please clarify the diagnosis and the genetic and/or biological basis to support the diagnosis in these cases. Also please clarify if there are any differences between these patients at presentation and the patients who had poor outcomes that might predict clinical response.**

6. **In the September 19, 2014 meeting you stated that your intent was primarily to improve liver function in the patients with PD. Please clarify the indication you seek for the PD population.**

7. **You have provided the median ALT and AST values (natural log) of SED or PD over time in Figure 2 on Page 74, Section 11.4.1.2 of Study CAC 91-10-10. Please also provide the median spot figures of**

**ALT and AST (natural log) over time of for 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz of SED defects. Also, provide the median spot figures of ALT and AST for Zellweger's and Neonatal Adrenoleukodystrophy, Refsum's, and type unknown of PD patients.**

8. **Provide the median spot figures of total bilirubin and weight percentile values for SED, 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz defects; and PD, Zellweger's, Neonatal Adrenoleuko-dystrophy, Refsum's, and Type unknown defects.**

9. **Please consider additional ways of graphically displaying data by subgroup that may be beneficial in interpreting individual patient data and response to treatment (e.g., waterfall plots).**

10. **Please provide data to support a dose range and details of dose adjustment procedures (i.e., how soon to recheck transaminases, bilirubin and urine FAB-MS after dose initiation) and provide a patient management algorithm. Please provide specific examples of dose adjustment (stating dose in mg/kg) with clinical data and FAB-MS graphs to support dose adjustment decisions.**

11. **Please reconfigure the Dosage and Administration Section and group the information into 3 sections:**

    **2.1 Dosage Regimen**

    **2.2 Administration Instructions**

    **2.3 Dose Titration and Monitoring (to include therapeutic monitoring information to assess effectiveness and/or safety that currently appears in section 5.1)**

*12.* **Do not include references to published articles in Section 15. The only types of references to be included are described in the regulations (21 CFR 201.57):** ***When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.***

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Monday, September 29, 2014 1:35 PM
**To:** Strongin, Brian K

**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205-750 Cholic Acid Clinical Information Request

Brian,

Do you have any updates on your message below? We haven't received anything since.

Thanks

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
**Sent:** Wednesday, September 24, 2014 3:12 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** RE: NDA 205-750 Cholic Acid Clinical Information Request

We need to revise a few of these information requests and will send a revised version later today or early tomorrow. Sorry about the confusion. Thanks.

---

**From:** Strongin, Brian K
**Sent:** Tuesday, September 23, 2014 4:05 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** NDA 205-750 Cholic Acid Clinical Information Request

Please respond to this information request ASAP. Thanks.

**Provide the definition of "Cholestasis" and provide the rationale for treating patients with Peroxisomal Disease (PD) and normal urinary bile acids at baseline. Also, provide the rationale for treating PD patients with normal bilirubin, or normal transaminases at baseline. In your submission, we see some PD patients (PIDs 7, 11, 17, 19, 29, 30, 51, 64, and 92) had normal urinary bile acid at baseline. Some of them also had normal total bilirubin or near normal transaminases at baseline.**

**Some of the patients with PD had reversible increases of transaminases shortly after bile acid therapy (PIDs 7, 11, 64, and 69) or non-reversible increase after the treatment (PID 21). Please explain the potential causes of the worsening in transaminases.**

**In the September 19, 2014 meeting you stated that your intent was primarily to palliate the patients with PD. Please clarify the indication you seek for the PD population.**

**The 48% (14/29) of the patients in the PD population died at a young age. However we note apparently different outcomes in some patients (012, 020, 021, 046, and 092). Please clarify any differences between these patients and the patients who had poor outcomes. Please also explain the reason patient 051 was treated despite normal transaminases and normal urine bile acids at age 10 years. Please justify this treatment approach.**

**You have provided the median ALT and AST values (natural log) of SED or PD over time in Figure 2 on Page 74, Section 11.4.1.2 of Study CAC 91-10-10. Please also provide the median spot figures of ALT and AST (natural log) over time of for 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz of SED defects. Also, provide the median spot figures of ALT and AST for Zellweger's and Neonatal Adrenoleukodystrophy, Refsum's, and type unknown of PD patients.**

**Provide the median spot figures of total bilirubin and weight percentile values for SED, 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz defects; and PD, Zellweger's, Neonatal Adrenoleuko-dystrophy, Refsum's, and Type unknown defects.**

**Please provide data to support a dose range and details of dose adjustment procedures (i.e., how soon to recheck transaminases, bilirubin and urine FAB-MS after dose initiation) and provide a patient management algorithm. Please provide specific examples of dose**

**adjustment (stating dose in mg/kg) with clinical data and FAB-MS graphs to support dose adjustment decisions.**

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/s/

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BRIAN K STRONGIN
10/01/2014

**From:** Strongin, Brian K
**To:** Gary Pasternack; "Kellie Kennon"
**Cc:** Strongin, Brian K
**Subject:** RE: NDA 205-750 Cholic Acid Clinical Information Request
**Date:** Tuesday, September 30, 2014 12:19:11 PM

Here is the revised clinical information request. Please respond ASAP and let me know if you have any questions. Thanks.

1. **You used the term "cholestasis" in several different ways in the narratives referencing both urine and clinical abnormalities. Provide the definition(s) of the term "Cholestasis" as used in your narratives.**

2. **Provide the rationale for treating patients with Peroxisomal Disease (PD) and normal urinary bile acids at baseline. In your submission, some PD patients (PIDs 7, 11, 17, 19, 29, 30, 51, 64, and 92) had normal urinary bile acid at baseline. Some of these patients also had normal total bilirubin or near normal transaminases at baseline.**

3. **Provide the rationale for treating PD patients with normal bilirubin, or normal transaminases at baseline (e.g., patient 051).**

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5. **Forty-eight percent (14/29) of the patients in the PD population died at a young age. However, we note different outcomes with longer life span in some cases (PIDs 012, 020, 021, 046, and 092) and in some cases reports of "normal function". Please clarify the diagnosis and the genetic and/or biological basis to support the diagnosis in these cases. Also please clarify if there are any differences between these patients at presentation and the patients who had poor outcomes that might predict clinical response.**

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**ALT and AST (natural log) over time of for 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz of SED defects. Also, provide the median spot figures of ALT and AST for Zellweger's and Neonatal Adrenoleukodystrophy, Refsum's, and type unknown of PD patients.**

8. **Provide the median spot figures of total bilirubin and weight percentile values for SED, 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz defects; and PD, Zellweger's, Neonatal Adrenoleuko-dystrophy, Refsum's, and Type unknown defects.**

9. **Please consider additional ways of graphically displaying data by subgroup that may be beneficial in interpreting individual patient data and response to treatment (e.g., waterfall plots).**

10. **Please provide data to support a dose range and details of dose adjustment procedures (i.e., how soon to recheck transaminases, bilirubin and urine FAB-MS after dose initiation) and provide a patient management algorithm. Please provide specific examples of dose adjustment (stating dose in mg/kg) with clinical data and FAB-MS graphs to support dose adjustment decisions.**

11. **Please reconfigure the Dosage and Administration Section and group the information into 3 sections:**

    **2.1 Dosage Regimen**

    **2.2 Administration Instructions**

    **2.3 Dose Titration and Monitoring (to include therapeutic monitoring information to assess effectiveness and/or safety that currently appears in section 5.1)**

*12.* **Do not include references to published articles in Section 15. The only types of references to be included are described in the regulations (21 CFR 201.57):** ***When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.***

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Monday, September 29, 2014 1:35 PM
**To:** Strongin, Brian K

**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205-750 Cholic Acid Clinical Information Request

Brian,

Do you have any updates on your message below? We haven't received anything since.

Thanks

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



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**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
**Sent:** Wednesday, September 24, 2014 3:12 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** RE: NDA 205-750 Cholic Acid Clinical Information Request

We need to revise a few of these information requests and will send a revised version later today or early tomorrow. Sorry about the confusion. Thanks.

---

**From:** Strongin, Brian K
**Sent:** Tuesday, September 23, 2014 4:05 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** NDA 205-750 Cholic Acid Clinical Information Request

Please respond to this information request ASAP. Thanks.

**Provide the definition of "Cholestasis" and provide the rationale for treating patients with Peroxisomal Disease (PD) and normal urinary bile acids at baseline. Also, provide the rationale for treating PD patients with normal bilirubin, or normal transaminases at baseline. In your submission, we see some PD patients (PIDs 7, 11, 17, 19, 29, 30, 51, 64, and 92) had normal urinary bile acid at baseline. Some of them also had normal total bilirubin or near normal transaminases at baseline.**

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**Provide the median spot figures of total bilirubin and weight percentile values for SED, 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz defects; and PD, Zellweger's, Neonatal Adrenoleuko-dystrophy, Refsum's, and Type unknown defects.**

**Please provide data to support a dose range and details of dose adjustment procedures (i.e., how soon to recheck transaminases, bilirubin and urine FAB-MS after dose initiation) and provide a patient management algorithm. Please provide specific examples of dose**

**adjustment (stating dose in mg/kg) with clinical data and FAB-MS graphs to support dose adjustment decisions.**

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/s/

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BRIAN K STRONGIN
09/30/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | NDA 205-750 Cholic Acid Clinical Information Request |
| **Date:** | Tuesday, September 23, 2014 4:04:48 PM |

Please respond to this information request ASAP. Thanks.

**1. Provide the definition of "Cholestasis" and provide the rationale for treating patients with Peroxisomal Disease (PD) and normal urinary bile acids at baseline. Also, provide the rationale for treating PD patients with normal bilirubin, or normal transaminases at baseline. In your submission, we see some PD patients (PIDs 7, 11, 17, 19, 29, 30, 51, 64, and 92) had normal urinary bile acid at baseline. Some of them also had normal total bilirubin or near normal transaminases at baseline.**

**2. Some of the patients with PD had reversible increases of transaminases shortly after bile acid therapy (PIDs 7, 11, 64, and 69) or non-reversible increase after the treatment (PID 21). Please explain the potential causes of the worsening in transaminases.**

**3. In the September 19, 2014 meeting you stated that your intent was primarily to palliate the patients with PD. Please clarify the indication you seek for the PD population.**

**4. The 48% (14/29) of the patients in the PD population died at a young age. However we note apparently different outcomes in some patients (012, 020, 021, 046, and 092). Please clarify any differences between these patients and the patients who had poor outcomes. Please also explain the reason patient 051 was treated despite normal transaminases and normal urine bile acids at age 10 years. Please justify this treatment approach.**

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**6. Provide the median spot figures of total bilirubin and weight percentile values for SED, 3β-HSD, AKR1D1, CTX, AMACR, CYP7A1, and Smith-Lemli-Opitz defects; and PD, Zellweger's, Neonatal Adrenoleuko-dystrophy, Refsum's, and Type unknown defects.**

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/s/

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BRIAN K STRONGIN
09/23/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | FW: NDA 205750 |
| **Date:** | Tuesday, September 16, 2014 5:58:13 PM |

Here are our responses to your questions:

The principal impact of the date ambiguities is on the graphs, which often look worse as a result of excluding data points with incomplete dates. The first question is does the Agency wish us to impute complete dates that would allow addition of the excluded data to the graphical presentations. If the answer is yes, how does the Agency wish the imputation to be carried out?

1) You can impute the 15th of the month if you do not know the date, but should flag those that are imputed.

The second question where we need the Agency's guidance concerns the missing bilirubin data that was the subject of your e-mail of September 5, 2014. We have retrieved all of the missing data from the site. Approximately 60% of the data is not from source. Does the Agency wish us to include the non-source data? If the answer is yes, we will include all instances where both values and units were discernible. Finally, some of the bilirubin data contains incomplete date information. As in the first question, does the Agency wish us to impute dates for these data points and if so, how?

2) Yes, you can include bilirubin data not from source docs, but you also should flag which values do not have source documents.

Thanks.

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Friday, September 12, 2014 10:51 PM
**To:** Strongin, Brian K
**Cc:** 'Kellie Kennon'
**Subject:** NDA 205750

Brian,

I am pleased to let you know that all of the remaining patient narratives have been uploaded to the FDA system. I am writing, however to seek the Agency's guidance on a couple of issues.

The cover letter for submission SN034 contained the following text, which pertains to all narratives submitted including those that were uploaded today:

> *Data listings are included for each patient in addition to the graphical presentations to aid in review. For some patient assessments only a partial date such as month and year was*

*available in the source documentation. Patient assessments with incomplete dates are not be included in the graphs, since proper representation of the data point on the graph requires a complete assessment date.*

*For the statistical analyses, patient assessments with incomplete dates could be used for some analyses. In cases where a month and year were present, the information was sufficient to determine whether the data represented a pre- or post-treatment value. In analyses that did not depend upon the date per se, but only upon the knowledge that the data was obtained pre- or post- treatment, all such data were employed in the analyses and therefore appear in the listings. An example of such analyses would be the* (b) (4) *analogous analyses. However, other analyses required full date information. Examples include the graphs included in each patient analysis, where time is represented on the abscissa, and determinations of height and weight percentiles, which require a precise knowledge of patient age. Data points with incomplete date information were excluded from all analyses where complete date information was required. Therefore, some of the graphs contain fewer data points than the corresponding listings. This is intentional and represents the exclusion of data points with incomplete date information.*

The principal impact of the date ambiguities is on the graphs, which often look worse as a result of excluding data points with incomplete dates. The first question is does the Agency wish us to impute complete dates that would allow addition of the excluded data to the graphical presentations. If the answer is yes, how does the Agency wish the imputation to be carried out?

The second question where we need the Agency's guidance concerns the missing bilirubin data that was the subject of your e-mail of September 5, 2014. We have retrieved all of the missing data from the site. Approximately 60% of the data is not from source. Does the Agency wish us to include the non-source data? If the answer is yes, we will include all instances where both values and units were discernible. Finally, some of the bilirubin data contains incomplete date information. As in the first question, does the Agency wish us to impute dates for these data points and if so, how?

Thanks as always for your help.

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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/s/

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BRIAN K STRONGIN
09/16/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | ECTD: NDA205750 Cholic Acid Clinical Information Request |
| **Date:** | Friday, September 12, 2014 3:49:44 PM |

Please respond to this request ASAP.

Please refer to your August 8, 2014 submission including letters from parents and patients received from the Council for Bile Acid Deficiency Diseases. Please provide the patient ID numbers for the patients that were the subjects of these letters.

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/s/

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BRIAN K STRONGIN
09/12/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | Information Request for NDA 205750 Cholic Acid |
| **Date:** | Tuesday, August 19, 2014 5:21:47 PM |

Please respond to the information request below ASAP. Thanks.

Provide detailed information of the neurologic evaluation of patients with peroxisomal disorder at baseline in Studies CAC 92-8-19 and CAC 91-10-10; Provide detailed narratives of the neurological follow-up assessment (improvement or deterioration) during the CA treatment.

Thanks.

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/s/

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BRIAN K STRONGIN
09/12/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | NDA 20570 Cholbam (Cholic Acid) Information Request |
| **Date:** | Friday, September 05, 2014 11:00:28 AM |

This application is a 505(b)(2) NDA that relies on published literature for the following labeling sections: 7 Drug Interactions, 12 Clinical Pharmacology, and 13 Nonclinical. Please submit a revised Form FDA 356H with the 505(b)(2) box in section 17 checked. Thanks.

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/s/

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BRIAN K STRONGIN
09/05/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | NDA 205-750 Cholic Acid Clinical Information Request |
| **Date:** | Friday, September 05, 2014 8:12:45 AM |

Please respond to this information request ASAP.

Please provide the data on bilirubin levels that was not provided in the study report or your data sets as noted in the inspection report (see table attached). Provide this data in the narratives and graphical presentation of the patient data that you are currently working on. Also, please reanalyze the trial data for the bilirubin results by subtype for the subtypes that are affected by this new data.

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/s/

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BRIAN K STRONGIN
09/05/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | Clinical Information Request |
| **Date:** | Thursday, August 28, 2014 10:29:11 AM |

Please respond to this information request ASAP.

Please provide information about the registry you have in Europe for Cholic Acid. Provide the protocol and a summary of any data that have been collected to date.

Thanks.

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/s/

---

BRIAN K STRONGIN
08/28/2014

## Strongin, Brian K

**From:** Strongin, Brian K
**Sent:** Wednesday, August 27, 2014 6:04 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** Follow-Up to 8/25/14 Pre-Late Cycle Meeting - NDA 205750 Cholic Acid

If possible, please have James E. Heubi, MD and Kenneth D.R. Setchell, Ph.D call into the September 19 Late Cycle Teleconference. Thanks.

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/s/

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BRIAN K STRONGIN
08/27/2014

## Strongin, Brian K

**From:** Strongin, Brian K
**Sent:** Friday, August 22, 2014 2:45 PM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** FW: Information Request for NDA 205-750 Cholic acid
**Attachments:** f_alt_911010_91-10-10-009.rtf

**Importance:** High

The graphs you have proposed are acceptable. Thanks.

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Thursday, August 21, 2014 6:27 PM
**To:** Strongin, Brian K
**Cc:** 'Kellie Kennon'
**Subject:** RE: Information Request for NDA 205-750 Cholic acid
**Importance:** High

Brian,

We are now working on the request that you sent earlier today. It would be helpful if the Agency could verify that the graphs that will be provided as part of the narratives for each patient are consistent with what the Agency has in mind. I have attached a sample graph for ALT. Similar graphs would be provided for each of the additional parameters, namely AST, Bilirubin total and direct, urine bile acid evaluations, and growth in height and weight. Each graph would have vertical lines denoting start and stop dates of cholic acid, and separate, distinct, vertical lines for urso start and stop dates.

Is the above acceptable to the Agency for the graphical component of each narrative?

Thanks,

Best
Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
O: +1 410.545.0494 ext 107 | F: +1 866.339.3910 | M: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

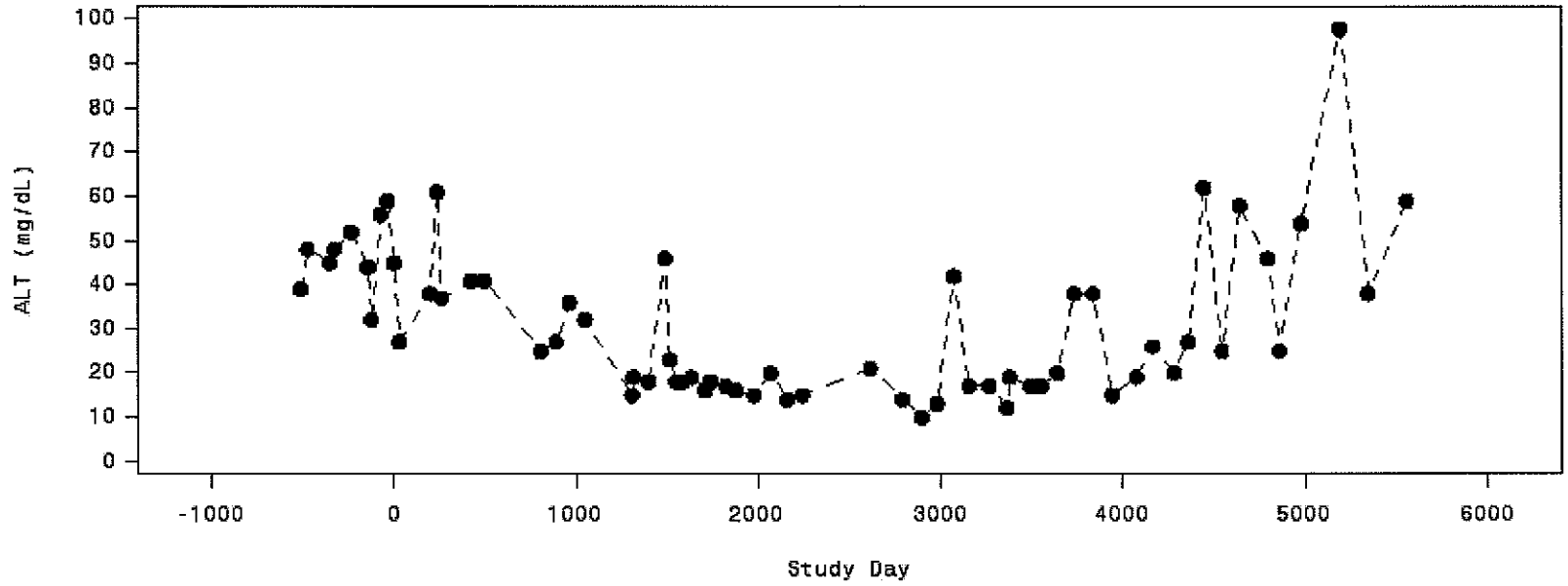
**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
**Sent:** Thursday, August 21, 2014 9:28 AM
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** Information Request for NDA 205-750 Cholic acid

Please respond to this information request no later than September 12, 2014. The information we are requesting now is included in the August 18 information request, so you can just ignore that one and provide everything in this one. You can give it to us in groups by subtype as you finish them so we can evaluate the data faster.

> Provide individual patient narratives for all patients in your application for whom you have not previously submitted a narrative. Identify each patient by subtype of disorder, and group narratives by subtype. Provide pre-treatment baseline information on dose, start date, dose changes, and concomitant medications, including ursodeoxycholic acid (URSO), physical exams, clinical course, and outcome. For peroxisomal disorder (PD) patients, include neurological exams and documentation of improvement or decline in neuro-cognitive function, and very long-chain fatty acids (VLFA) at baseline and follow-up. For each graphical patient profile, display data for, ALT AST, Bilirubin total and direct, urine bile acid evaluations, and growth in height and weight over time. Indicate start and stop dates for cholic acid (and URSO) on the graphs.

Thanks and let me know if you have any questions.

ALT (mg/dL) Results (91-10-10)
Defect Subgroup: 3B-HSD or HSD3B7
Subject: 91-10-10-009



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/s/

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BRIAN K STRONGIN
08/25/2014

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** Information Request for NDA 205-750 Cholic acid
**Date:** Thursday, August 21, 2014 9:28:28 AM

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Please respond to this information request no later than September 12, 2014. The information we are requesting now is included in the August 18 information request, so you can just ignore that one and provide everything in this one. You can give it to us in groups by subtype as you finish them so we can evaluate the data faster.

> Provide individual patient narratives for all patients in your application for whom you have not previously submitted a narrative. Identify each patient by subtype of disorder, and group narratives by subtype. Provide pre-treatment baseline information on dose, start date, dose changes, and concomitant medications, including ursodeoxycholic acid (URSO), physical exams, clinical course, and outcome. For peroxisomal disorder (PD) patients, include neurological exams and documentation of improvement or decline in neuro-cognitive function, and very long-chain fatty acids (VLFA) at baseline and follow-up.
> For each graphical patient profile, display data for ALT, AST, Bilirubin total and direct, urine bile acid evaluations, and growth in height and weight over time. Indicate start and stop dates for cholic acid (and URSO) on the graphs.

Thanks and let me know if you have any questions.

---

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/s/

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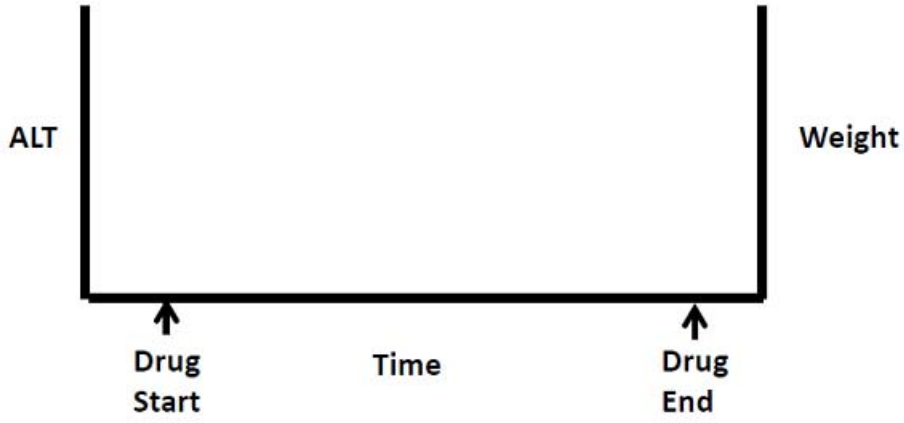
BRIAN K STRONGIN
08/21/2014

**Strongin, Brian K**

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **Sent:** | Monday, August 18, 2014 4:49 PM |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | Information Request for NDA 205-750 Cholic acid |

Please respond to this information request ASAP. E-mail the response to me and follow with a submission to your NDA. Thanks.

To better understand the time course of weight and ALT changes in patients, please provide a graphical presentation for each patient of interest (see below) from the CAC-91-10-10 trial using the example figure shell displayed below (i.e., one graphical output per patient). Express ALT in mg/dL and weight as a percentile of normal. Provide the starting and stopping time of cholic acid treatment if they are available, however provide an explanation if these data are not available. Please provide these graphical outputs by diagnosis subgroup, and begin with the 28 3β-HSD patients first. Please send the results of each subgroup as you finish the analysis.



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/s/

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BRIAN K STRONGIN
08/18/2014

| | |
|---|---|
| **From:** | Barley, Stacy |
| **To:** | "kellie.kennon@asklepionpharm.com"; "gary.pasternack@asklepionpharm.com" |
| **Subject:** | FW: NDA 205750 Cholbam (cholic acid): Information Request |
| **Date:** | Thursday, August 14, 2014 4:22:00 PM |
| **Attachments:** | NDA 205750 cholic acid Tables.doc<br>NDA 205750 cholic acid Tables.pdf |

Hello:

Please refer to your New Drug Application (NDA) dated and received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We are in the process of reviewing your application and request additional information. Please complete the attached document.

We request a response by close of business August 19, 2014. Contact Brian Strongin on or after August 18th if you have any additional questions.

Thank you.

***Stacy Barley, RN, M.S.N., M.S.H.A.***

***CDR, USPHS Commissioned Corps***

***Senior Regulatory Project Manager***

***Division of Gastroenterology/Inborn Errors Products***

***Office of Drug Evaluation III***

***CDER/FDA***

***(301) 796-2137 (office)***

***(301) 796-9905 (fax)***

***stacy.barley@fda.hhs.gov***

**DGIEP Information Request:** Provide the appropriate outcomes to the corresponding space in the following two tables. DGIEP will evaluate the responder responses in ALT reduction and related changes of bilirubin, weight percentile, survival time, and treatment duration. If you do not have the data, provide explanations.

**SED Patients on Cholic Acid**

| ALT reduction from baseline | N (%) | Bilirubin change (mean, range) | Weight change (mean, range) | Survival (mean, range) | Treatment duration (mean, range) |
|---|---|---|---|---|---|
| At least 25% | X (x%) | | | | |
| At least 50% | Y (y%) | | | | |
| At least 75% | Z (z%) | | | | |

**PD Patients on Cholic Acid**

| ALT reduction from baseline | N (%) | Bilirubin change (mean, range) | Weight change (mean, range) | Survival (mean, range) | Treatment duration (mean, range) |
|---|---|---|---|---|---|
| At least 25% | X (x%) | | | | |
| At least 50% | Y (y%) | | | | |
| At least 75% | Z (z%) | | | | |

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STACY R BARLEY
08/14/2014

| | |
|---|---|
| **From:** | Barley, Stacy |
| **To:** | "kellie.kennon@asklepionpharm.com" |
| **Cc:** | Strongin, Brian K |
| **Subject:** | FW: NDA 205750 Cholbam (cholic acid): Information |
| **Date:** | Tuesday, August 12, 2014 4:18:00 PM |

Hello Kellie:

Please refer to your New Drug Application (NDA) dated and received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

Additionally, please refer to the email from Anissa Davis-Williams dated June 20, 2014 (shown below) which extended the labeling and postmarketing requirement/commitment discussion date until August 5, 2014.

I am covering for Brian Strongin this week and this email serves as a response to your inquiry below regarding the status of the labeling review. The review is ongoing and we predict labeling discussion will not be available for you until mid-September. Please contact Brian Strongin on or after August 18th if you have any additional questions.

Thank you.

***Stacy Barley, RN, M.S.N., M.S.H.A.***
***CDR, USPHS Commissioned Corps***
***Senior Regulatory Project Manager***
***Division of Gastroenterology/Inborn Errors Products***
***Office of Drug Evaluation III***
***CDER/FDA***
***(301) 796-2137 (office)***
***(301) 796-9905 (fax)***
***stacy.barley@fda.hhs.gov***


---

**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Thursday, August 07, 2014 5:02 PM
**To:** Strongin, Brian K
**Cc:** Gary Pasternack
**Subject:** FW: NDA 205750 Cholbam (cholic acid): Information

Good afternoon Brian,

I wanted to follow-up on the email below to see if there was any information regarding the our proposed labeling. I realize that the timeline was extended to August 5, 2014 but I don't believe we have received anything at this point. Thank you in advance.

Regards,

Kellie A. Kennon, BSN | Clinical Research Director |

**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Friday, June 20, 2014 9:48 AM
**To:** Gary Pasternack
**Cc:** Kellie Kennon
**Subject:** NDA 205750 Cholbam (cholic acid): Information

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

Additionally, please refer to the "Review Extension-Major Amendment" letter dated February 27, 2014 regarding the communication date for which the agency is to convey proposed labeling, and if necessary, any Postmarketing requirement/commitment requests by July 21, 2014.

Due to our ongoing review of the information requests and response submissions received, the agency will not be able to provide you with the edited labeling or Postmarketing requirement/commitment until August 5, 2014.

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*

*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

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/s/

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STACY R BARLEY
08/12/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K; Ishihara, Richard; Gao, Wen-Yi; Dimick, Lara L |
| **Subject:** | NDA 205750 Cholic Acid Clinical Information Request |
| **Date:** | Sunday, August 03, 2014 10:04:48 AM |

Please respond to the information request below ASAP:

You provided 16 letters from the parents of 9 patients (6 SED patients and 3 PD patients) to address quality of life on July 11, 2014 (Suppl. 0029). However, you did not provide the narratives of the 9 patients to support the letters. Provide the narratives of PIDs 012, 092, 132 including the clinical outcomes, liver biopsy results (if available), and laboratory tests for the FDA review.

Thanks.

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/s/

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BRIAN K STRONGIN
08/03/2014

## Strongin, Brian K

**From:** Strongin, Brian K
**Sent:** Wednesday, July 30, 2014 1:10 PM
**To:** kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K; Gao, Wen-Yi; Dimick, Lara L
**Subject:** NDA 205750 Cholic Acid - Clinical Information Request

Please respond to this information request ASAP.

Provide data analyses similar to what has already been submitted on 4/4/2014, 4/25/2014, 5/6/2014, 5/23/2014, and 7/7/2014. These analyses should compare median baseline to median post-treatment AND last baseline to last post-treatment for the following efficacy parameters:

- ALT and AST
  - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result
  - Categorical data analysis i.e., display counts for Below ULN, 1 to <2 ULN, 2 to <3 ULN, >=3 ULN along with CMH test result
- Bilirubin (Total, Direct, and Indirect)
  - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result
  - Categorical data analysis i.e., display counts for <=ULN, >ULN along with CMH test result
- Height and Weight
  - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result

The analysis for these parameters should be conducted within the following subgroup:

- Subset of Single Enzyme Defect (SED) patients from the CAC-91-10-10 study: 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) and Δ4-3-oxosteroid 5β-reductase

As was the case for the deliverable submitted on 7/7/2014, please perform your analysis on both the ITT and the mITT populations.

Thanks.

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/s/

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BRIAN K STRONGIN
07/30/2014

## Strongin, Brian K

**From:** Strongin, Brian K
**Sent:** Tuesday, July 22, 2014 5:24 PM
**To:** kellie.kennon@asklepionpharma.com
**Subject:** Fw: USAN Application for Cholic Acid - NDA 205750

Your reply is acceptable.

---

**From**: Holbert, Gene W
**Sent**: Tuesday, July 22, 2014 05:01 PM Eastern Standard Time
**To**: Strongin, Brian K
**Cc**: Kowblansky, Marie
**Subject**: RE: USAN Application for Cholic Acid - NDA 205750

That's all I need. Thanks.

---

**From:** Strongin, Brian K
**Sent:** Tuesday, July 22, 2014 5:01 PM
**To:** Kowblansky, Marie
**Cc:** Holbert, Gene W; kellie.kennon@asklepionpharm.com
**Subject:** Re: USAN Application for Cholic Acid - NDA 205750

Please let me know if this response is ok. Thanks.

---

**From**: Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent**: Tuesday, July 22, 2014 03:38 PM Eastern Standard Time
**To**: Strongin, Brian K
**Cc**: Kowblansky, Marie; Holbert, Gene W; 'Kellie Kennon' <kellie.kennon@asklepionpharm.com>
**Subject**: RE: USAN Application for Cholic Acid - NDA 205750

Brian,

Cholic acid was adopted by USAN on March 26, 2014 per the attached Adoption Statement. The USAN listing (BC-106), also attached, is available from the USAN website at the link shown below:

http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/adopted-names.page.

The USAN office has confirmed that this became official as of the date of adoption. However, the USP dictionary is only updated annually. Therefore, the name will appear in the 2015 revision of the dictionary.

We will file this information to the NDA in the next e-CTD submission.

Please let me know if this is satisfactory, or if you need further information.

Thanks,

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
**Sent:** Tuesday, July 22, 2014 11:14 AM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** Kowblansky, Marie; Holbert, Gene W; Strongin, Brian K
**Subject:** RE: USAN Application for Cholic Acid - NDA 205750

Please give me an update on the status of your application for cholic acid as a USAN name. Thanks.

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Monday, January 27, 2014 2:43 PM
**To:** Davis, Anissa
**Cc:** 'Kellie Kennon'
**Subject:** USAN Application for Cholic Acid - NDA 205750

Commander Davis,

Just want to confirm that Asklepion has applied for the USAN listing for cholic acid. Dr Stephanie Shubat, Director, USAN can provide confirmation if such is required by the Agency.

Thanks very much –

Best
Gary Pasterack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

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729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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BRIAN K STRONGIN
07/23/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**GENERAL ADVICE**

Asklepion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, MD, Ph.D.
Chief Executive Officer
750 East Pratt Street, Suite 360
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cholbam (cholic acid) Capsules, 50mg and 250mg.

We also refer to the Agency's Mid-Cycle Communication dated May 26, 2014 from the May 20, 2014 teleconference with you.

We also refer to your July 11, 2014 letter asking the Agency to amend the Mid-Cycle communication.

We have reviewed the referenced material and will add the following sentence to the Additional Discussion section on page 6 of the Mid-Cycle Communication:

> The sponsor suggested that additional information could be provided from patients/parents on their viewpoint of the efficacy of Cholbam. The Division replied that the sponsor may submit this information and the Division would attempt to review it as time allowed. However, it would be considered as anecdotal supportive information only.

If you have any questions, call Brian Strongin, R.Ph., MBA; Chief, Regulatory Project Management Staff, at (301) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Andrew Mulberg, M.D.
Deputy Director
Division of Gastroenterology and
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment: May 26, 2014 Mid-Cycle Communication

9 Page(s) has been Withheld as this is a duplicate copy of Mid-Cycle Communication found on e-p 201 of this review immediately following this page

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ANDREW E MULBERG
07/17/2014

**From:** Strongin, Brian K
**To:** kellie.kennon@asklepionpharm.com
**Cc:** Lee, Sue Chih H; Kim, Insook; Strongin, Brian K
**Subject:** RE: NDA 205750 Cholbam (cholic acid): Clinical Pharmacology Information Request
**Date:** Thursday, July 03, 2014 1:41:29 PM

Please respond to the following questions ASAP. Thanks.

1. Please clarify if the treatment is marked as "on-going", meaning that the treatment is on-going as of today.

2. Please clarify if the liquid formulation is still being administered. It is noted that the treatment is on-going for several patients who are on the liquid formulation.

3. Please clarify whether cholic acid was instructed to be given with food.

Thanks

---

**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Thursday, July 03, 2014 6:52 AM
**To:** Strongin, Brian K; Sarchet, Jennifer
**Cc:** Kim, Insook; Lee, Sue Chih H; Gary Pasternack
**Subject:** NDA 205750 Cholbam (cholic acid): Clinical Pharmacology Information Request
**Importance:** High

Good morning Brian and Jennifer,

Please find the requested Cholic Acid Medication Listings for 91-10-10. Our statistician created two listings; one for subjects with Single Enzyme Defects and a second for subjects with Peroxisomal Disorders.

These two listings will be formally submitted to the application on Monday July 7, 2014, along with analyses for a separate Clinical Information request.

Please let me know if you have any questions.

Regards,

Kellie A. Kennon, BSN | Clinical Research Director |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

---

**From:** Kellie Kennon
**Sent:** Wednesday, July 02, 2014 8:51 AM
**To:** Strongin, Brian K
**Cc:** Kim, Insook; Lee, Sue Chih H; Gary Pasternack
**Subject:** RE: NDA 205750 Cholbam (cholic acid): Clinical Pharmacology Information Request
**Importance:** High

Hello Brian,

We apologize for this oversight. There was some confusion on our part upon receipt of the first information request.

We will provide the tabulation for 91-10-10 as soon as possible.

Thanks,
Kellie

Kellie A. Kennon, BSN | Clinical Research Director |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Strongin, Brian K [mailto:Brian.Strongin@fda.hhs.gov]
**Sent:** Tuesday, July 01, 2014 4:37 PM
**To:** Gary Pasternack
**Cc:** Strongin, Brian K; Kellie Kennon; Kim, Insook; Lee, Sue Chih H
**Subject:** FW: NDA 205750 Cholbam (cholic acid): Clinical Pharmacology Information Request
**Importance:** High

Please respond to the information request below ASAP.

Please provide a tabulated list of formulations (capsule and/or oral solution) and the regimen

used by each patient in Study CAC 91-10-10.

Thanks.

APPEARS THIS WAY ON ORIGINAL

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/s/

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BRIAN K STRONGIN
07/04/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com |
| **Cc:** | Strongin, Brian K; kellie.kennon@asklepionpharm.com; Kim, Insook; Lee, Sue Chih H |
| **Subject:** | FW: NDA 205750 Cholbam (cholic acid): Clinical Pharmacology Information Request |
| **Date:** | Tuesday, July 01, 2014 4:36:37 PM |
| **Importance:** | High |

Please respond to the information request below ASAP.

Please provide a tabulated list of formulations (capsule and/or oral solution) and the regimen used by each patient in Study CAC 91-10-10.

Thanks.

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/s/

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BRIAN K STRONGIN
07/01/2014

| | |
|---|---|
| **From:** | Sarchet, Jennifer |
| **To:** | "Kellie Kennon"; Gary Pasternack |
| **Cc:** | Barley, Stacy; Strongin, Brian K |
| **Subject:** | RE: NDA 205750; Cholbam (cholic acid) capsules; Information Request June 24, 2014 |
| **Date:** | Friday, June 27, 2014 1:39:01 PM |

Dear Dr. Pasternack and Ms. Kennon,

Please perform your analysis on both the ITT and the mITT populations. If you have any additional questions, please do not hesitate to contact me.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)



---

**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Friday, June 27, 2014 9:15 AM
**To:** Gary Pasternack; Sarchet, Jennifer
**Cc:** Barley, Stacy
**Subject:** RE: NDA 205750; Cholbam (cholic acid) capsules; Information Request June 24, 2014

Jennifer,

Would it be possible to confirm whether the division would like to see these analyses performed in the mITT or ITT population?

Many thanks,

Kellie A. Kennon, BSN | Clinical Research Director |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Thursday, June 26, 2014 12:06 PM
**To:** 'Sarchet, Jennifer'
**Cc:** 'Barley, Stacy'; Kellie Kennon
**Subject:** RE: NDA 205750; Cholbam (cholic acid) capsules; Information Request June 24, 2014

Thanks VERY much.

Best
Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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**CONFIDENTIALITY WARNING: This message and any attachments are intended only for the use of the intended recipient(s), are confidential, and may be privileged. If you are not the intended recipient, you are hereby notified that any review, retransmission, conversion to hard copy, copying, circulation or other use of this message and any attachments is strictly prohibited. If you are not the intended recipient, please notify the sender immediately by return e-mail, and delete this message and any attachments from your system. The sender cannot guarantee that this email or any attachment to it is free of computer viruses or other conditions which may damage or interfere with data, hardware or software with which it might be used.**

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**From:** Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
**Sent:** Thursday, June 26, 2014 11:55 AM
**To:** 'Gary Pasternack'
**Cc:** Barley, Stacy
**Subject:** RE: NDA 205750; Cholbam (cholic acid) capsules; Information Request June 24, 2014

Dr. Pasternack,

Yes, a response by July 7, 2014 to our information request dated June 24, 2014 is acceptable.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)



---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Thursday, June 26, 2014 10:04 AM
**To:** Sarchet, Jennifer
**Cc:** kellie.kennon@asklepionpharm.com; Barley, Stacy
**Subject:** RE: NDA 205750; Cholbam (cholic acid) capsules; Information Request June 24, 2014

Jennifer,

We have reviewed the request of 24 June with our statistical team. As you are likely aware, we are currently preparing a substantive submission for 30 June. Our statistical team tells us that they do not have the capacity to work on the 24 June request until the submission for 30 June is finalized. Given the intercession of the coming Fourth of July holiday, we respectfully request extension of the deadline from 1 July to 7 July. Please let me know if this is acceptable to the Agency.

Thanks & best regards,

Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
**gary.pasternack@asklepionpharm.com**


729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Sarchet, Jennifer [mailto:Jennifer.Sarchet@fda.hhs.gov]
**Sent:** Tuesday, June 24, 2014 12:50 PM
**To:** 'gary.pasternack@asklepionpharm.com'
**Cc:** 'kellie.kennon@asklepionpharm.com'; Barley, Stacy
**Subject:** NDA 205750; Cholbam (cholic acid) capsules; Information Request June 24, 2014

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We have the following clinical information request:

Clinical IR on June 23, 2014
(1) Provide data analyses similar to what has already been submitted on 4/4/2014, 4/25/2014, 5/6/2014, and 5/23/2014. These analyses should compare median baseline to median post-treatment AND last baseline to last post-treatment for the following efficacy parameters:

- ALT and AST
    - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result
    - Categorical data analysis i.e., display counts for Below ULN, 1 to <2 ULN, 2 to <3 ULN, >=3 ULN along with CMH test result
- Bilirubin (Total, Direct, and Indirect)
    - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result

- Categorical data analysis i.e., display counts for <=ULN, >ULN along with CMH test result

- Height and Weight
  - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result

The analyses for these parameters should be conducted separately within the following five subgroups as follows:

1. Subset of Single Enzyme Defect (SED) patients from the CAC-91-10-10 study: 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD)
2. Subset of SED patients from the CAC-91-10-10 study: Δ4-3-oxosteroid 5β-reductase
3. Subset of SED patients from the CAC-91-10-10 study: Sterol 27-hydroxylase (CTX)
4. Subset of Peroxisomal (PD) patients from the CAC-91-10-10 study: Zellweger syndrome
5. Subset of PD patients from the CAC-91-10-10 study: Neonatal adrenoleukodystrophy

(2) Please conduct exploratory comparative analyses for the following two parameters.

- Overall Death Rate (using Fisher's Exact Test)
- Time-to-Death from Birth (using a traditional Kaplan Meier approach along with the log-rank test)

The analyses for these two parameters should be conducted separately within the following seven subgroups as follows:

1. All CAC-91-10-10 SED patients vs. all Historical Control (HC) SED patients
2. All CAC-91-10-10 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) patients vs. all HC 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) patients
3. All CAC-91-10-10 Δ4-3-oxosteroid 5β-reductase patients vs. all HC Δ4-3-oxosteroid 5β-reductase patients
4. All CAC-91-10-10 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) and Δ4-3-oxosteroid 5β-reductase patients vs. all HC 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) and Δ4-3-oxosteroid 5β-reductase patients
5. All CAC-91-10-10 Sterol 27-hydroxylase (CTX) patients vs. all HC Sterol 27-hydroxylase (CTX) patients
6. All CAC-91-10-10 Zellweger syndrome patients vs. all HC Zellweger syndrome patients
7. All CAC-91-10-10 Neonatal adrenoleukodystrophy patients vs. all HC Neonatal adrenoleukodystrophy patients

Please additionally submit a corresponding Kaplan-Meier survival analysis figure/plot for

each of the seven requested Time-to-Death from Birth survival analyses specified above.

Please submit your exact copies of the official submission to me via e-mail as well as an official submission to the application by July 1, 2014.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

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/s/

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JENNIFER S SARCHET
06/27/2014

| | |
|---|---|
| **From:** | Sarchet, Jennifer |
| **To:** | "gary.pasternack@asklepionpharm.com" |
| **Cc:** | "kellie.kennon@asklepionpharm.com"; Barley, Stacy |
| **Subject:** | NDA 205750; Cholbam (cholic acid) capsules; Information Request June 24, 2014 |
| **Date:** | Tuesday, June 24, 2014 12:50:03 PM |

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We have the following clinical information request:

Clinical IR on June 23, 2014

(1) Provide data analyses similar to what has already been submitted on 4/4/2014, 4/25/2014, 5/6/2014, and 5/23/2014. These analyses should compare median baseline to median post-treatment AND last baseline to last post-treatment for the following efficacy parameters:

- ALT and AST
  - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result
  - Categorical data analysis i.e., display counts for Below ULN, 1 to <2 ULN, 2 to <3 ULN, >=3 ULN along with CMH test result
- Bilirubin (Total, Direct, and Indirect)
  - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result
  - Categorical data analysis i.e., display counts for <=ULN, >ULN along with CMH test result
- Height and Weight
  - Continuous data analysis i.e., display n, Mean, SE, STD, Median, Min, Max along with t-test result

The analyses for these parameters should be conducted separately within the following five subgroups as follows:

1. Subset of Single Enzyme Defect (SED) patients from the CAC-91-10-10 study: 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD)
2. Subset of SED patients from the CAC-91-10-10 study: Δ4-3-oxosteroid 5β-reductase
3. Subset of SED patients from the CAC-91-10-10 study: Sterol 27-hydroxylase (CTX)
4. Subset of Peroxisomal (PD) patients from the CAC-91-10-10 study: Zellweger syndrome
5. Subset of PD patients from the CAC-91-10-10 study: Neonatal adrenoleukodystrophy

(2) Please conduct exploratory comparative analyses for the following two parameters.

- Overall Death Rate (using Fisher's Exact Test)

- Time-to-Death from Birth (using a traditional Kaplan Meier approach along with the log-rank test)

The analyses for these two parameters should be conducted separately within the following seven subgroups as follows:

1. All CAC-91-10-10 SED patients vs. all Historical Control (HC) SED patients
2. All CAC-91-10-10 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) patients vs. all HC 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) patients
3. All CAC-91-10-10 Δ4-3-oxosteroid 5β-reductase patients vs. all HC Δ4-3-oxosteroid 5β-reductase patients
4. All CAC-91-10-10 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) and Δ4-3-oxosteroid 5β-reductase patients vs. all HC 3β-hydroxy-5-C27-steroid dehydrogenase (3β-HSD) and Δ4-3-oxosteroid 5β-reductase patients
5. All CAC-91-10-10 Sterol 27-hydroxylase (CTX) patients vs. all HC Sterol 27-hydroxylase (CTX) patients
6. All CAC-91-10-10 Zellweger syndrome patients vs. all HC Zellweger syndrome patients
7. All CAC-91-10-10 Neonatal adrenoleukodystrophy patients vs. all HC Neonatal adrenoleukodystrophy patients

Please additionally submit a corresponding Kaplan-Meier survival analysis figure/plot for each of the seven requested Time-to-Death from Birth survival analyses specified above.

Please submit your exact copies of the official submission to me via e-mail as well as an official submission to the application by July 1, 2014.

Thank you,
Jennifer

Jennifer Sarchet RN, BSN
LCDR, U.S. Public Health Service Corps
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA
240-402-4275 (office)

**402-4275. Thank you.**

APPEARS THIS WAY ON ORIGINAL

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/s/

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JENNIFER S SARCHET
06/24/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, June 20, 2014 9:48 AM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 Cholbam (cholic acid): Information

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

Additionally, please refer to the "Review Extension-Major Amendment" letter dated February 27, 2014 regarding the communication date for which the agency is to convey proposed labeling, and if necessary, any Postmarketing requirement/commitment requests by July 21, 2014.

Due to our ongoing review of the information requests and response submissions received, the agency will not be able to provide you with the edited labeling or Postmarketing requirement/commitment until August 5, 2014.

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

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ANISSA A DAVIS
06/20/2014

**Davis, Anissa**

| | |
|---|---|
| **From:** | Davis, Anissa |
| **Sent:** | Thursday, June 19, 2014 9:51 PM |
| **To:** | gary.pasternack@asklepionpharm.com |
| **Cc:** | 'Kellie Kennon' (kellie.kennon@asklepionpharm.com) |
| **Subject:** | NDA 205750 Cholbam (cholic acid): Clinical Pharmacology Information Request |

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We are conducting a review of the clinical pharmacology section of your submission, to include labeling, and have the following information requests:

1) Please provide a tabulated list of dosage regimen, administration method and the CU and the to-be-marketed (TBM) formulation for each patient in Study CAC-001-01.
   - According to Section 9.4.5, the study drug was administered orally in divided doses (as determined by the investigator) for a total daily dose of 10-15 mg/kg body weight. Please clarify whether the dose was given in divided doses and the regimen was maintained after switching to the TBM formulation.
   - Clarify if oral solution was also used prior to switching to the to-be-marketed formulation in Study CAC-001-01.
   - Clarify how capsule was administered to patients especially to young patients. If cholic acid was mixed with soft food, please provide information on what type of soft food was used.

2) Please provide a tabulated list of formulations (capsule and/or oral solution) and regimen used by each patient and whether the to-be-marketed capsule formulation was used in Study CAC 91-10-10. Please clarify if some patients were switched to the TBM during Study CAC 91-10-10.

3) You propose that aluminum-based antacids be administered (b) (4) before and after CHOLBAM. Please provide supporting information (b) (4)

4) Provide a rationale and comprehensive summary of available information to support following labeling languages in Section 7 Drug Interactions. We request that the relevant information from recent publications also be included to support your labeling claim. Also, please provide a rationale for monitoring of serum and urinary bile acids with the anticipated results from drug interactions.

(b) (4)

(b) (4)

5) Provide information on the transporters and enzymes that are involved in the cholic acid metabolism and enter-hepatic circulation.

6) Provide information whether cholic acid and its conjugates can inhibit and/or induce CYP enzymes and transporters.

**Please submit your response officially to your application by Monday, June 23, 2014.**

Thank You!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

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ANISSA A DAVIS
06/19/2014

**Davis, Anissa**

---

**From:** Davis, Anissa
**Sent:** Friday, June 06, 2014 1:42 PM
**To:** gary.pasternack@asklepionpharm.com; 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Information Request

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We have the following clinical information request:

1. Please conduct exploratory comparative analyses for the following two parameters. Note that these analyses will be used for internal review only, and will not be intended to be supportive of efficacy.

    a. Overall Death Rate (using Fisher's Exact Test)

    b. Time-to-Death from Birth (using a traditional Kaplan Meier approach along with the log-rank test)

2. The analyses for these two parameters should be conducted separately within the following six subgroups as follows:

    a. All CAC-91-10-10 Peroxisomal Disorder (PD) patients vs. all Historical Control (HC) PD patients

    b. All CAC-91-10-10 PD patients who received exclusively a regimen of Cholic Acid only vs. all HC PD patients

    c. All CAC-91-10-10 PD patients who did not receive exclusively a regimen of Cholic Acid only vs. all HC PD patients

    d. All CAC-91-10-10 Single-Enzyme-Defect (SED) patients vs. all CAC-91-10-10 PD patients

    e. All CAC-91-10-10 SED patients who received exclusively a regimen of Cholic Acid only vs. all CAC-91-10-10 PD patients who received exclusively a regimen of Cholic Acid only

    f. All CAC-91-10-10 SED patients who did not receive exclusively a regimen of Cholic Acid only vs. all CAC-91-10-10 PD patients who did not receive exclusively a regimen of Cholic Acid only

3. Please additionally submit a corresponding Kaplan-Meier survival analysis figure/plot for each of the six requested Time-to-Death from Birth survival analyses specified above.

**Please submit your responses officially to your application by June 20, 2014.**

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

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/s/

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ANISSA A DAVIS
06/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**MID-CYCLE COMMUNICATION**

Askelpion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, M.D., Ph.D.
Chief Executive Officer
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

Dear Dr. Pasterneck:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal) Food, Drug, and Cosmetic Act for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We also refer to the teleconference between representatives of your firm and the FDA on May 20, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call me at (301) 796-5016.

Sincerely,

*{See appended electronic signature page}*

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Mid-Cycle Communication

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MID-CYCLE COMMUNICATION

**Meeting Date and Time:** May 20, 2014

**Application Number:** NDA 205750
**Product Name:** Cholbam (cholic acid)
**Indication:** [redacted] (b) (4)

**Applicant Name:** Asklepion Pharmaceuticals, Inc.

**Meeting Chair:** Dr. Lara Dimick-Santos
**Meeting Recorder:** CDR Anissa Davis-Williams

**FDA ATTENDEES**

Office of Drug Evaluation III

| | |
|---|---|
| Julie Beitz, M.D. | Director |
| Amy Eagan, M.D. | Deputy Director |

Division of Gastroenterology and Inborn Errors Products

| | |
|---|---|
| Andrew E. Mulberg, M.D., F.A.A.P. | Deputy Director |
| Joyce Korvick, M.D., M.P.H. | Deputy Director for Safety |
| Lara Dimick-Santos, M.D. | Medical Team Lead |
| Wen-Yi Gao, M.D. | Medical Reviewer |
| David Joseph, Ph.D. | Pharmacology Team Lead |
| Brian Strongin, R.Ph., M.B.A. | Chief, Project Management Staff |

CDR Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
Senior Regulatory Project Manager

Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3

| | |
|---|---|
| Sue-Chih Lee, Ph.D. | Team Lead |
| Insook Kim, Ph.D. | Clinical Pharmacology Reviewer |

Office of New Drug Quality Assessment/ Division of New Drug Quality Assessment II

| | |
|---|---|
| Gene Holbert, Ph.D. | Chemistry Reviewer |
| Kareen Riviere, Ph.D. | Biopharmaceutics Reviewer |
| John Duan, Ph.D. | Biopharmaceutics Reviewer |

Division of Biometrics III

| | |
|---|---|
| Behrang Vali, M.S. | Statistical Reviewer |

Pediatric and Maternal Health Staff

Ethan Hausman, M.D. Medical Officer
Tamara Johnson, M.D. Medical Officer
Denise Pica-Branco, Ph.D. Senior Regulatory Health Project Manager

Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation
George Neyarapally, Pharm.D., M.P.H., Drug Risk Management Analyst

Office of Compliance/ Division of Good Clinical Practice Assessment
Susan Thompson, M.D. Team Leader

Office of Surveillance and Epidemiology/Division of Pharmacovigilance I
Kimberly Swank, Pharm. D. Reviewer

Office of Surveillance and Epidemiology/Division of Epidemiology 1
Carolyn McCloskey, M.D., M.P.H., Medical Officer Epidemiologist

**EASTERN RESEARCH GROUP ATTENDEES**
So Hyun Kim Independent Assessor

**APPLICANT ATTENDEES**
Gary Pasternack, M.D., Ph.D., CEO
Kellie A. Kennon, B.S.N., Clinical Research Director
(b) (4) Regulatory Consultant
(b) (4) NDA Submission Lead
Ken Roberts, Business Operations Manager
(b) (4)

## 1.0 INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

## 2.0 SIGNIFICANT REVIEW ISSUES

**We have concerns about the poor quality of the data submitted and apparent missing data in your application, as follows:**

- **The data submitted are incomplete for some of the endpoints in the trial and for many of the patients; for example:**

- **7 of 14 death narratives are missing for PD patients**
- **only 12 of the SED and 12 of the PD patients have comparative pre- and post-treatment direct bilirubin results**
- **only 8 SED patients have matching histology data from pre- and post-treatment**

- **The source documentation for many of the laboratory values cannot be verified.**
- **Shipping records are missing from 1993 to October of 1995, and some shipping records were not accurately recorded as late as 2009, making verification that some patients were administered drug impossible.**

**We are also concerned that the baseline characteristics of patients in your historical control group do not appear to match the baseline characteristics of the patients in the trial.**

***Additional Discussion:***
***Asklepion asked for clarification regarding death narratives and the need for the bilirubin data. FDA explained that the critical information for safety review of the death narratives is missing. For example, in some of the death narratives, dosing regimen (cholic acid alone or in combination with URSO), dose levels, dosing duration, post-treatment evaluation, and cause of death evaluation are not presented. FDA also explained that bilirubin data are needed since the data in the original submission are poor. For example, in the original submission, (1) the bilirubin data of the single enzyme defect patients were mixed with that of the peroxisomal disorder; and (2) the data were based on laboratory visits. Some of patients who had only pre-treatment bilirubin were used to show the improvement by treatment. FDA also stated that both direct and indirect bilirubin results are needed for review. Asklepion stated they will attempt to provide the requested information.***

***Asklepion stated that the baseline characteristics of Cholbam patients did not match most of the patients from the historical control because the Cholbam patients were not diagnosed until late in the course of their disease.***

## 2.1 CLINICAL

- The clinical review identified a potential safety issue. Cholic Acid-treatment associated cholestasis and deaths cannot be excluded. There were 6 patients (ID numbers 0, 16, 103, 127, 143, and 152) in the SED group who died during Study CAC-91-01-10. The average age at death was younger than in the

historical untreated control group. Narrative analysis shows that the 6 patients had cholestasis, with elevated LFTs and bilirubin levels during treatment prior to their deaths.

- We do not agree (b) (4)

- We do not agree with your assessment of the paper by Keane et al., because beta-oxidation of fatty acid is an essential mitochondrial pathway for producing ATP for the survival of hepatocytes. "Swollen mitochondria" from hepatic cells is evidence of cell injury, and signals dysfunction (inability to produce ATP), H+ accumulation, and delayed mitochondrial toxicity. We disagree with the comment that the mitochondrial change is a "fixation artifact". This is generally considered to be an irreversible change by pathologists. Consistent with the results reported with this animal model is the high death rate in the PD population reported in your trial.

***Additional Discussion:***
***Asklepion will respond, in writing to the agency, regarding the Keane et al. article.***

## 2.2 CLINICAL PHARMACOLOGY

- We do not think that the FAB-MS assay of urinary bile acids was validated for quantitative analysis to provide a reliable assessment of the change in urinary bile acids. As you noted in the SOP and validation report, the method was developed only for qualitative assessment to determine the presence and absence of certain mass peaks. We acknowledge that you provided comparisons between the FAB-MS assay and a recently developed LC/ESI/MS/MS assay to support the semi-quantitative nature of your FAB-MS based analysis. Nevertheless, (b) (4) makes the evaluation of change in the level of urinary bile acids unreliable.

## 2.3 STATISTICS

- There are no significant statistical issues identified to date.

## 2.4 CHEMISTRY

- There are no significant chemistry issues identified to date.

## 2.5 BIOPHARMACEUTICS

We have the following concerns about Study CAC-003-01:

- The justification provided (b) (4) is not adequate (b) (4)

(b) (4)

(b) (4)

## 2.6 NONCLINICAL

- There are no significant nonclinical issues identified to date.

## 3.0 INFORMATION REQUESTS (IRs)

Outstanding IRs

| IR | Date Sent | Date Due |
|---|---|---|
| **Clinical** | **May 8, 2014** | **June 16, 2014** |

| | | |
|---|---|---|
| **Clinical** | **May 15, 2014** | **May 26, 2014** |
| **Chemistry/Biopharmaceutics** | **May 15, 2014** | **June 5, 2014** |
| **Product Packaging Facility Amendment** | | **May 30, 2014** |

***Additional Discussion:***
***Asklepion asked if the response to the Clinical IR sent on May 15, 2014 can be split into two submissions. FDA agreed.***

## 4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

- There is currently no need for a Risk Evaluation and Mitigation Strategy (REMS)

## 5.0 ADVISORY COMMITTEE (AC) MEETING PLANS

- There are no plans at this time for an AC meeting.

## 6.0 LATE-CYCLE MEETING/OTHER PROJECTED MILESTONES

- The proposed date for the Late Cycle Meeting (LCM) is August 19, 2014.
    - **Other Projected Milestones**

      Labeling, PMR/PMC to Applicant: July 21, 2014
      LCM Background Package: August 7, 2014
      PDUFA Action: October 21, 2014

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/s/

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ANISSA A DAVIS
05/26/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, May 23, 2014 8:26 AM
**To:** 'gary.pasternack@asklepionpharm.com'
**Cc:** ''Kellie Kennon' (kellie.kennon@asklepionpharm.com)'
**Subject:** RE: NDA 205750: Clinical Information Request Add on to 5/15/14

**Importance:** High

Hello Dr. Pasternack:
In regard to the Information Request previously sent to you on 5/15/2014 for NDA 205750 (see below), please additionally submit a corresponding Kaplan-Meier survival analysis figure/plot for each of the six requested Time-to-Death from Birth survival analyses.

Thank you.

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***



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**From:** Davis, Anissa
**Sent:** Thursday, May 15, 2014 10:32 AM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Information Request

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

1. Please conduct comparative analyses between patients from the CAC-91-10-10 study and those who are part of your natural history cohort for the following two parameters:

    a. Overall Death Rate (using Fisher's Exact Test)
    b. Time-to-Death from Birth (using a traditional Kaplan Meier approach along with the log-rank test)

2. The analyses for these two parameters should be conducted separately within the following six subgroups as follows:

    a. All CAC-91-10-10 Single-Enzyme-Defect (SED) patients who received exclusively a regimen of Cholic Acid only vs. all Historical Control (HC) SED patients
    b. All CAC-91-10-10 SED patients who did not receive exclusively a regimen of Cholic Acid only vs. all HC SED patients
    c. All CAC-91-10-10 3-Beta and Delta patients who received exclusively a regimen of Cholic Acid only vs. all HC 3-Beta and Delta patients
    d. All CAC-91-10-10 3-Beta and Delta patients who did not receive exclusively a regimen of Cholic Acid only vs. all HC 3-Beta and Delta patients
    e. All CAC-91-10-10 3-Beta patients who received exclusively a regimen of Cholic Acid only vs. all HC 3-Beta patients
    f. All CAC-91-10-10 3-Beta patients who did not receive exclusively a regimen of Cholic Acid only vs. all HC 3-Beta patients

3. Repeat all analyses previously submitted on 4/4/2014, 4/25/2014, and 5/6/2014 for urinary bile acids, ALT/AST, bilirubin, and height/weight using the mITT analysis population.

4. Provide the individual dosing regimen and duration for all the patients in single enzyme defect group and the peroxisomal disorder group. The information should include the daily dose of Cholic Acid and URSO, the combined total dose, and the dosing duration. Include this information for all patients who died.

5. Provide the patient ID noted as Case 1 of historical sibling control.

**Please submit your responses officially to your application by May 26, 2014.**

Thank You!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
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ANISSA A DAVIS
05/23/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Thursday, May 15, 2014 10:32 AM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Information Request

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

1. Please conduct comparative analyses between patients from the CAC-91-10-10 study and those who are part of your natural history cohort for the following two parameters:

    a. Overall Death Rate (using Fisher's Exact Test)
    b. Time-to-Death from Birth (using a traditional Kaplan Meier approach along with the log-rank test)

2. The analyses for these two parameters should be conducted separately within the following six subgroups as follows:

    a. All CAC-91-10-10 Single-Enzyme-Defect (SED) patients who received exclusively a regimen of Cholic Acid only vs. all Historical Control (HC) SED patients
    b. All CAC-91-10-10 SED patients who did not receive exclusively a regimen of Cholic Acid only vs. all HC SED patients
    c. All CAC-91-10-10 3-Beta and Delta patients who received exclusively a regimen of Cholic Acid only vs. all HC 3-Beta and Delta patients
    d. All CAC-91-10-10 3-Beta and Delta patients who did not receive exclusively a regimen of Cholic Acid only vs. all HC 3-Beta and Delta patients
    e. All CAC-91-10-10 3-Beta patients who received exclusively a regimen of Cholic Acid only vs. all HC 3-Beta patients
    f. All CAC-91-10-10 3-Beta patients who did not receive exclusively a regimen of Cholic Acid only vs. all HC 3-Beta patients

3. Repeat all analyses previously submitted on 4/4/2014, 4/25/2014, and 5/6/2014 for urinary bile acids, ALT/AST, bilirubin, and height/weight using the mITT analysis population.

4. Provide the individual dosing regimen and duration for all the patients in single enzyme defect group and the peroxisomal disorder group. The information should include the daily dose of Cholic Acid and URSO, the combined total dose, and the dosing duration. Include this information for all patients who died.

5. Provide the patient ID noted as Case 1 of historical sibling control.

**Please submit your responses officially to your application by May 26, 2014.**

Thank You!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
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*Senior Regulatory Project Manager*
*Food and Drug Administration*
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***Anissa.Davis@fda.hhs.gov***

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/s/

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ANISSA A DAVIS
05/15/2014

## Tran-Zwanetz, Catherine

**From:** Tran-Zwanetz, Catherine
**Sent:** Thursday, May 15, 2014 10:26 AM
**To:** 'Gary Pasternack'
**Cc:** Davis, Anissa
**Subject:** NDA 205750 CMC IR

Hello Dr. Pasternack,

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. You have not provided adequate data/justification to support a paddle speed of 100 rpm in your proposed dissolution method. We recommend that you adopt a paddle speed of (b) (4) rpm for your dissolution method.
2. Based on the mean in-vitro dissolution profile data for all strengths, it appears that the proposed dissolution acceptance criterion (b) (4) Q = (b) (4) % at 15 minutes. Provide dissolution data for the stability batches at the 15 minute time-point.
3. Provide comparative dissolution with f2 testing for the drug product manufactured at Patheon (b) (4) and Patheon France using Apparatus 2, (b) (4) rpm paddle speed, 500 ml, pH 6.8 for the 50 mg strength and Apparatus 2, (b) (4) rpm paddle speed, 900 ml, pH 6.8 for the 250 mg strength to support.
4. We note several issues with the design and conduct of Study CAC-003-01 that are concerning (b) (4) To continue with our review, provide evidence either with your own data or literature data to justify why the proposed study design should be considered adequate for review. Your response should also explain the clinical relevance of the different Cmax levels observed for the pharmacy capsule formulation and to-be marketed capsule formulation.

5. Your process description (module 3.2.P.3.3) and in-process controls (module 3.2.P.3.4) indicate that (b) (4) Resolve this discrepancy.

6. No in-process controls (b) (4) are described (section 3.2.P.4). Amend this section to include the in-process tests performed (b) (4) and their acceptance criteria.

7. The COA for (b) (4) Reference Standard is not adequate. The acceptance criteria list only Appearance, Melting Point and Elemental Analyses. Criteria should also include a specific identity test, such as an IR spectrum. Add a specific identity test.

Please provide this information as an email and an amendment to the NDA submission by Thursday, June 5, 2014. Please let me know if you have any questions.

Thanks,
Cathy Tran-Zwanetz
Regulatory Project Manager
(301) 796-3877

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/s/

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CATHERINE A TRAN-ZWANETZ
05/15/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**MEETING PRELIMINARY COMMENTS**

Asklepion Pharmaceuticals, LLC
Attention: Kellie A. Kennon, BSN
Clinical Research Director
729 E. Pratt Street, Suite 360
Baltimore, MD 21202

Dear Ms. Kennon:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cholic Acid Capsules.

We also refer to your, correspondence, received May 5, 2014, requesting a meeting (b) (4)

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, call me, at (301) 796-3877.

Sincerely,

*{See appended electronic signature page}*

Cathy Tran-Zwanetz
Regulatory Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# PRELIMINARY MEETING COMMENTS

**Meeting Type:** C
**Meeting Category:** CMC

**Application Number:** NDA 205750
**Product Name:** Cholic Acid Capsules
**Indication:** (b) (4)

**Sponsor/Applicant Name:** Asklepion Pharmaceuticals LLC

**Introduction:**
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting .We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

## 1.0 BACKGROUND

The purpose of this meeting was to discuss (b) (4) The Agency and applicant previously had a teleconference to discuss concerns (b) (4)

## 2.0 DISCUSSION

**Proposal** (b) (4)

**Asklepion Pharmaceuticals, LLC proposes** (b) (4)

(b) (4)

**1. Will the Agency accept** (b) (4) **?**

*FDA RESPONSE:*
*The Agency will accept* (b) (4)

**Concurrence (b) (4) to be Submitted**

(b) (4)

**2. Does the Agency agree that the proposed (b) (4) is sufficient?**

*FDA RESPONSE:*
*The outlined data package is acceptable. In addition, please provide a memo* (b) (4)

**Concurrence (b) (4)**

(b) (4)

(b) (4)

**3. Does the Agency agree** (b) (4) **?**

*FDA RESPONSE:*

(b) (4)

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CATHERINE A TRAN-ZWANETZ
05/13/2014

**Davis, Anissa**

| | |
|---|---|
| **From:** | Davis, Anissa |
| **Sent:** | Thursday, May 08, 2014 11:59 AM |
| **To:** | gary.pasternack@asklepionpharm.com |
| **Cc:** | 'Kellie Kennon' (kellie.kennon@asklepionpharm.com) |
| **Subject:** | NDA 205750 (cholic acid): Clinical Information Request |

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

**We have the following clinical information request:**

**During the inspection of the clinical sites, FDA identified that the following clinical investigators did not have the financial disclosure forms:**

1. **Samuel Kocoshis, MD located at Pittsburgh Children's Hospital, Pittsburgh, PA (Subject #009 was enrolled at this site in 1993).**
2. **Hisham Nazer, MD, Head of Pediatric Gastroenterology and Clinical Nutrition, King Faisal Hospital and Research Center, Riyadh, Saud Arabia (Subject #009 was followed-up at this site from 1995 through).**
3. **Mohammaed Othman Banemai, MBBS located at King Faisal Specialist Hospital (Performed study related procedures and dispensed test article to Subject #009 from August 2001 through September 2004).**
4. **Erick Hernandex, MD located at University of Miami School of Medicine, Miami, FL (Subject #106 was enrolled at this site on November 28, 2006).**
5. **Milton Scharff, MD located at Camelback Pediatrics in Phoenix, AZ (Subject #57 was enrolled in the study at the site)."**

**Please submit the financial disclosure forms for the above investigators as well as for any investigators who treated subjects, provided subject data that was included in the clinical study report, or to whom product was shipped.**

**Please submit officially to your application by June 16, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
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ANISSA A DAVIS
05/08/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Tuesday, April 29, 2014 6:14 PM
**To:** gary.pasternack@asklepionpharm.com; 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Pharmacology Information Request

**Importance:** High

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We have the following clinical pharmacology information requests:

1) Please provide raw data used to generate the atypical urinary bile acid graph in Figure 9 of "Interpretation of urinary FAB-MS spectra for the diagnosis of genetic defects in bile acid synthesis".

   It is unclear how many patients provided data for each time point and what was the signal-to-noise ratio from each patient to support one data point. Please provide data in a tabulated format. Please also explain how ULN was defined in the Figure for atypical urinary BA.

2) It was noted that for some patients, (b) (4) Please provide any possible explanation, if any (b) (4) ?

**Please submit your responses to me via email and officially to your application by April 30, 2014.**

Thank you!

Anissa

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
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ANISSA A DAVIS
04/29/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Monday, April 28, 2014 10:35 PM
**To:** 'Kellie Kennon'
**Cc:** Gary Pasternack; Todd Eggleston
**Subject:** RE: NDA 205750 Cholbam(cholic acid): Clinical Information Request-FDA Response

**Importance:** High

Hello Kellie and Dr. Pasternack:

Below are FDA responses, **in red,** to your questions/responses emailed 4/28/14.

1. FDA Request: "You have not defined the term ">ULN" and "<ULN" in the submitted bilirubin tables. Provide the reference range and reference units (e.g., mg/dL or mol/L) for these values."
    a. Revised tables which include the mg/dL and ULN will be provided.

**FDA Response: Noted**

2. FDA Request: "Bilirubin (Direct, Indirect, and Total) is a continuous variable. We also need to review the total data without ULN-sub-grouped. Provide the median, mean, SD, SE, and n with no imputation by single enzyme defects or peroxisomal disorders."
    a. Bilirubin tables that include all elements requested were submitted to the application on April 4, 2014. Standard Error (SE) was the only statistic not included. Can you verify whether the reviewer would like the tables resent with Standard Error added?

| Title |
|---|
| Bilirubin, Summary of Baseline and Post-Treatment Results, ITT with No Imputation, Bile Acid Disease Population: Single Enzyme Defects (91-10-10) |
| Bilirubin, Summary of Baseline and Post-Treatment Results, ITT with No Imputation, Bile Acid Disease Population: Peroxisomal Disorders (91-10-10) |

**FDA Response: Yes. Send the requested tables with Standard Error.**

3. FDA Request: "Do not include [redacted] (b) (4) analyses. We will review the data of "Median Baseline to Median Post-Treatment", "Last Baseline to Last Post-Treatment" and "Mean Baseline to Mean Post-Treatment".

4.
    a. The "Median Baseline to Median Post-Treatment", "Last Baseline to Last Post-Treatment" and "Mean Baseline to Mean Post-Treatment" rows were previously submitted. Can you please clarify whether you want these tables resubmitted simply removing the [redacted] (b) (4) analyses?

**FDA Response: Yes. Resubmit the requested tables (1) without the [redacted] (b) (4) analyses; (2) with definitions of "UNL" for analysis of bilirubin as categorical variable; and (3) new tables for analysis of bilirubin as continuous variable.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
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*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***



---

**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Monday, April 28, 2014 11:05 AM
**To:** Davis, Anissa
**Cc:** Gary Pasternack; Todd Eggleston
**Subject:** RE: NDA 205750 Cholbam(cholic acid): Clinical Information Request
**Importance:** High

Good morning Anissa,

We have reviewed and discussed the bilirubin request with our statistician and would kindly request clarification on the following:

1. FDA Request: "You have not defined the term ">ULN" and "<ULN" in the submitted bilirubin tables. Provide the reference range and reference units (e.g., mg/dL or mol/L) for these values."
    a. Revised tables which include the mg/dL and ULN will be provided.
2. FDA Request: "Bilirubin (Direct, Indirect, and Total) is a continuous variable. We also need to review the total data without ULN-sub-grouped. Provide the median, mean, SD, SE, and n with no imputation by single enzyme defects or peroxisomal disorders."
    a. Bilirubin tables that include all elements requested were submitted to the application on April 4, 2014. Standard Error (SE) was the only statistic not included. Can you verify whether the reviewer would like the tables resent with Standard Error added?

| Title |
|---|
| Bilirubin, Summary of Baseline and Post-Treatment Results, ITT with No Imputation, Bile Acid Disease Population: Single Enzyme Defects (91-10-10) |
| Bilirubin, Summary of Baseline and Post-Treatment Results, ITT with No Imputation, Bile Acid Disease Population: Peroxisomal Disorders (91-10-10) |

3. FDA Request: "Do not include [redacted] (b) (4) analyses. We will review the data of "Median Baseline to Median Post-Treatment", "Last Baseline to Last Post-Treatment" and "Mean Baseline to Mean Post-Treatment".
4.
    a. The "Median Baseline to Median Post-Treatment", "Last Baseline to Last Post-Treatment" and "Mean Baseline to Mean Post-Treatment" rows were previously submitted. Can you please clarify whether you want these tables resubmitted simply removing the [redacted] (b) (4) analyses?

Thank-you in advance Anissa.

Kellie A. Kennon, BSN | Clinical Research Director |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: [redacted] (b) (6) |
kellie.kennon@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Friday, April 25, 2014 2:48 PM
**To:** Gary Pasternack
**Cc:** Kellie Kennon
**Subject:** NDA 205750 Cholbam(cholic acid): Clinical Information Request
**Importance:** High

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We also refer to your submission dated April 25, 2014 containing your responses to the clinical information requests dated April 7, 2014 and April 10, 2014.

We have the following comments and clinical information requests:

1. You have not defined the term ">ULN" and "<ULN" in the submitted bilirubin tables. Provide the reference range and reference units (e.g., mg/dL or mol/L) for these values. If different laboratories were used for different patients you should provide the individual patient reference ranges.

2. Bilirubin (Direct, Indirect, and Total) is a continuous variable. We also need to review the total data without ULN-sub-grouped. Provide the median, mean, SD, SE, and n with no imputation by single enzyme defects or peroxisomal disorders.

3. Do not include [redacted] (b) (4) analyses. We will review the data of "Median Baseline to Median Post-Treatment", "Last Baseline to Last Post-Treatment" and "Mean Baseline to Mean Post-Treatment".

**Please submit your responses officially to your application by May 2, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
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ANISSA A DAVIS
04/29/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, April 25, 2014 2:48 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 Cholbam(cholic acid): Clinical Information Request

**Importance:** High

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

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2. Bilirubin (Direct, Indirect, and Total) is a continuous variable. We also need to review the total data without ULN-sub-grouped. Provide the median, mean, SD, SE, and n with no imputation by single enzyme defects or peroxisomal disorders.

3. Do not include [redacted] (b) (4) analyses. We will review the data of "Median Baseline to Median Post-Treatment", "Last Baseline to Last Post-Treatment" and "Mean Baseline to Mean Post-Treatment".

**Please submit your responses officially to your application by May 2, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
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***Anissa.Davis@fda.hhs.gov***

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ANISSA A DAVIS
04/25/2014

**INSPECTIONAL ASSIGNMENT**
**(EMAIL TRANSMITTAL)**

| | |
|---|---|
| ***Date:*** | April 23, 2014 |
| ***To:*** | International:<br>Division of Medical Products and Tobacco Inspections<br>Office of Regulatory Affairs |
| ***Facility:*** | (b) (4)<br>FEI No.: (b) (4) |
| ***Drug Name (dosage form, strength):*** | Cholic Acid, Drug Substance |
| ***Profile Class:*** | (b) (4) |
| ***A/NDA No.:*** | NDA 205750 |
| ***Chemistry Reviewer*** | Gene Holbert, PhD<br>CDER/OPS/ONDQA/DNDQAII/BRIV<br>Gene.holbert@fda.hhs.gov, tel: (301) 796-1368 |
| ***Microbiology Reviewer*** | Bryan Riley, PhD<br>CDER/OPS/NDMS<br>Bryan.riley@fda.hhs.gov, tel: (301) 796-1595 |
| ***OC Compliance Officer*** | Christina Capacci-Daniel, PhD<br>CDER/OC/OMPQ/DGMPA<br>christina.capacci-daniel@fda.hhs.gov, tel: (301) 796-3532 |

CDER has identified specific area(s) for inspectional focus for drug substance manufacturing in connection with the NDA 205750 cholic acid 50mg and 250mg mg hard capsule. In accordance with the API Process Inspections Compliance Program 7356.002F and Pre-Approval Inspection Program Compliance Program 7346.832, PAIs provide for continuity in our pre-market review of drug products by focusing on areas in which the data is questionable; drug characteristics or sensitivities[1] indicate special scrutiny, the overall manufacturing and control strategy appears lacking; and potential manufacturing weaknesses may exist.

[1] Examples include heat, moisture, oxygen, or light sensitivity, as well as hygroscopicity, polymorphs, particle size, or other physical characteristics

**Summary of Product:**

NDA 205750 Cholic acid, 50mg and 250mg hard capsules, was submitted by Asklepion Pharmaceuticals LLC Corporation. Cholic acid is proposed [redacted] The absence of primary bile acids causes hepatocytes to continuously metabolize cholesterol in an attempt to establish a normal bile acid pool. The result is the continued production of high concentrations of these hepatotoxic metabolites, which cause a progressive cholestatic hepatitis and, if untreated, may lead to death from cirrhosis and liver failure. Cholic Acid has been granted Orphan Drug Designation. This product is currently approved in the EU. Children and adults will be taking cholic acid chronically for the treatment of these disorders.

Cholic acid commercial drug substance is manufactured by [redacted] the subject of this KTM. [redacted]

The cholic acid manufacturing process is described in DMF [redacted] All drug substance testing and stability studies are performed [redacted] Drug product manufacturing is completed at Patheon France in Bourgoin Jallieu, France.

The critical steps identified in the drug substance manufacturing process are [redacted] In Process Controls and Quality Parameters are listed in Appendix B.

**Summary of Manufacturing Process:**

[redacted]

(b) (4)

**Figure 1.** Drug Substance Manufacture Flowchart.


(b) (4)

[redacted]

**The following is a brief explanation of product or process specific issues that should receive follow-up during the inspection.**

## I. Chemistry Review

The Lead CMC Reviewer, Gene Holbert, PhD, has the following comment:

(b) (4)

[**OC Notes**: Please refer to III(a)(i) and (IV)(e)(i) for inspectional coverage]

## II. Microbiology Review

The Lead Microbiology Reviewer, Bryan Riley, PhD, has the following comment:

(b) (4)

[**OC Notes**: Please refer to III(a)(i) for inspectional coverage]

## III. Manufacturing

(b) (4)

3 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

A pre-inspection briefing may be scheduled if additional clarification or background is needed. Should you have questions prior to, during or post inspection, please contact the CDER officials identified above. The CDER Reviewer or Compliance Officer may participate in the inspection. If you would like to request someone from CDER to participate on the inspection, please contact CDER/OC.

Please report your findings regarding these issues in the Establishment Inspection Report (EIR) under the heading, "ADDITIONAL INFORMATION" with the subheading, "Follow-up to CDER PAI Questions."

**THIS ASSIGNMENT IS CONFIDENTIAL FDA CORRESONDENCE**

cc:
HFD-320 (Division Chron File)
HFD-323 (New and Generic Drug Manufacturing Team)
OC Doc No : KTM-2014-10

4 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

# Appendix C – Final Drug Substance Specification

## Table 1: Cholic Acid Finished Product Specification 01/1

| Test | Acceptance Criteria | Analytical Procedure |
|---|---|---|
| Appearance | White powder | Visual evaluation |
| Identification (FTIR) | The sample spectrum is concordant with that of a Cholic Acid reference standard. | FTIR spectroscopy |
| Identification (Melting Point) | (b) (4) | Melting Point Instrument |
| Specific Rotation (b) (4) | | Optical Polarimetry |
| (b) (4) | | (b) (4) |
| Acidity (dry basis) | | Acid/base titration |
| Assay (area % by HPLC) | | HPLC |
| Related Impurities: (b) (4) | | HPLC |
| Any Individual Unidentified Impurity<br>Total Unidentified Impurities<br>Total Related Impurities | | |
| (b) (4) | | (b) (4) |
| Heavy Metals (b) (4) | | Turbidimetric |
| Residual Solvents: (b) (4) | | Gas Chromatography |
| Microbiological:<br>Total Aerobic Microbial Count<br>Yeasts and Moulds<br>Escherichia coli | <br>Maximum (b) (4) cfu/g<br>Maximum (b) (4) cfu/g<br>Absent | Microbiological Examination |

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CHRISTINA A CAPACCI-DANIEL
04/23/2014

MAHESH R RAMANADHAM
04/23/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Thursday, April 10, 2014 6:22 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Information Request

**Importance:** High

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We have the following clinical information request:

1. Perform analysis by type of disease of bilirubin (direct bilirubin, Indirect bilirubin and total bilirubin) to compare Median Baseline to Median Post-Treatment and to compare Last Baseline to Last Post-Treatment, for both single enzyme defects and peroxisomal disorders, as you have presented for the liver function tests analysis.

**Please submit your responses to me via email and officially to your application by April 26, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
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***Anissa.Davis@fda.hhs.gov***

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/s/

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ANISSA A DAVIS
04/10/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Monday, April 07, 2014 5:34 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 Cholic Acid: Clinical Pharmacology Information Request
**Attachments:** Clin Pharm IR_040714.doc

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We acknowledge your submission of tabulated FAB Signal to Noise Ratio (91-10-10) on April 4, 2014; however, for ease of review, we would appreciate if the S/N ratio is presented in the format suggested in the attached file.

Please submit the dataset in an xpt file as well.

**Submit your responses to me via email and officially to your application by April 10, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
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*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

**Summary Table for Individual Patient Information organized by enzyme defect**

| Patient ID | Defect | Gender | Age at onset(?) | Dose (weight-based dose as well if available) |
|---|---|---|---|---|
| 91-10-10-001 | HSD3b7 | F | 8.12 | Unknown |
| 91-10-10-009 | HSD3b7 | M | 4.58 | Unknown<br>250 mg on 232 day post-dose and onward |
| 91-10-10-018 | HSD3b7 | F | 4.18 | Unknown |
| 91-10-10-024 | HSD3b7 | M | 0.82 | 75 mg |
| | | | | |
| 91-10-10-013 | Peroxisomal<br>Type unknown | F | 0.16 | 75 mg (day 61)<br>100 mg (Day 435) |
| | | | | |
| | | | | |

**Signal-to-Noise data for individual patient**

Example: For Patient 91-10-10-009

| Patient ID/ defect | Dose (mg) | Days | S/N | FAB Spectra Number | Remark as needed |
|---|---|---|---|---|---|
| 91-10-10-009/ HSD3b7 | Pre- | -436 | 20 | 924 | |
| | Pre- | -325 | 20 | 1024 | |
| | Pre- | -153 | 20 | 1119 | |
| | Pre- | -141 | 20 | 1164 | |
| | Pre- | -48 | 14 | 1250 | |
| | unknown | 17 | 4.5 | 1315 | |
| | unknown | 133 | 12 | 1415 | |
| | 250 | 232 | 3 | 1514 | |
| | 250 | 338 | 10 | 1628 | |
| | 250 | 427 | 6 | 1709 | |
| | 250 | 497 | 10 | 1785 | |
| | 250 | 602 | 2 | 1900 | |
| | 250 | 692 | 2 | 2034 | |
| | 250 | 792 | 4 | 2183 | |
| | 250 | 877 | 4 | 2293 | |
| | 250 | 948 | 8 | 2362 | |
| | 250 | 1032 | 3 | 2477 | |
| | 250 | 1517 | 20 | 3016 | |
| | 250 | 1594 | 8 | 3114 | |
| | 250 | 1637 | 3 | 3164 | |
| | 250 | 1714 | 8 | 3290 | |

| | | | | | |
|---|---|---|---|---|---|
| | 250 | 1742 | 4 | 3293 | |

APPEARS THIS WAY ON ORIGINAL

| Patient ID/ defect | Dose | Days | S/N | FABNum | Remark as needed |
|---|---|---|---|---|---|
| 91-10-10-013 | | -4 | 20 | | |
| | 75 mg | 61 | NA (impossible to determine S/N) | 835A | |
| | 100 mg | 435 | NA | 1143 | |

| Patient ID/ defect | Dose | Days | S/N | FABNum | Remark as needed |
|---|---|---|---|---|---|
| 91-10-10-016 | | No pre-data | | | |
| | | 6 | 15 | 2146 | |
| | | 21 | 20 | 2160 | |
| | | 23 | 3 | 2163 | |
| | | 43 | 4 | 2201 | |
| | | 65 | 2 | 2215 | |
| | | 70 | 2 | 2381 | |

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/s/

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ANISSA A DAVIS
04/07/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Monday, April 07, 2014 9:37 AM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 Cholbam (cholic acid): Clinical Information Request

**Importance:** High

Hello Pasternack:
Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We have the following clinical information request:

- If you performed studies in serum and urine, regarding comparisons of the levels of taurine-conjugated bile acids levels and glycine-bile acids in single enzyme defect patients with Cholic Acid treatment, please provide the data.

Please provide your response by April 26, 2014.

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
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ANISSA A DAVIS
04/07/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Thursday, April 03, 2014 1:57 PM
**To:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750

Hello Kellie:
Regarding your application NDA 205750, the date of our internal Mid-cycle meeting has been changed to May 6, 2014. The meeting schedule for the Post Mid-Cycle Meeting with Asklepion has been set for the following:

**Post Mid-Cycle Meeting w/Applicant**
Date: May 20, 2014
Time: 3:00 p.m. – 4:00 p.m.

Conference Information (you will need to contact me for any overseas numbers, if needed:

| | |
|---|---|
| **Toll Free/Freephone Number :** | (b) (4) |
| **Participant Passcode :** | (b) (4) |

Please contact me if you have any questions. Thank you.

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
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ANISSA A DAVIS
04/03/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Monday, March 31, 2014 11:47 AM
**To:** 'Kellie Kennon'
**Cc:** gary.pasternack@asklepionpharm.com
**Subject:** RE: NDA 205750: Response to 3/28/14 email

Hello Kellie:
Below is FDA's response **(in red)** to your question/clarification needed regarding subject 36 and/or discrepancy.

**Applicant email dated 3/28/14:**

> **Also, during our teleconference on March 14, 2014, the clinical reviewer requested that we confirm the diagnosis for subject 36. He indicated that upon review he had noted a discrepancy, but we are unable to locate any place whereby the subject is identified as having anything other than Zellwegers, which is one of the peroxisomal defects. Would it be possible to get additional information? We would very much like to correct any discrepancy, but have exhausted efforts to locate.**

**FDA Response 3/31/14:**

> **The submission states that Study CAC-91-10-10 only enrolled patients with single enzyme defect, while Study CAC-92-8-19 only enrolled patients with peroxisomal disorder. However, in our review, we note that there are 11 patients with peroxisomal disorder in Study CAC-91-10-10. The 11 patients who appear to have a diagnosis of peroxisomal disorder in Study CAC-91-10-10 have PID numbers of 13, 19, 30, 36, 72, 80, 123, 128, 130, 132, and 173. We also found that there are two patients with single enzyme defect in In Study CAC-92-8-19. These 2 patients have PID numbers of 27 and 76. Therefore, please do the following:**
>
> **1) Clarify if these patients are diagnosed correctly and are misclassified into the wrong study or if there is an error in the diagnosis.**
> **2) Please correct the errors and reanalyze the data sets with the patients appropriately classified with a correct diagnosis and into the correct study.**
> **3) Provide a complete safety analysis with patients stratified by the type of disease.**

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
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***Anissa.Davis@fda.hhs.gov***

---

**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Friday, March 28, 2014 1:02 PM
**To:** Davis, Anissa
**Subject:** RE: NDA 205750

Thanks Anissa. I just need the reviewer to identify where he discovered the discrepancy and/or clarify the patient number as we are looking at subject 36 and don't see a discrepancy.

Many thanks,

Kellie A. Kennon, BSN | Clinical Research Director |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Friday, March 28, 2014 12:57 PM
**To:** Kellie Kennon
**Subject:** RE: NDA 205750

Hello Kellie:
Thanks for the submission and the email. What additional information do you need from the clinical reviewer? Before sending the email to him, I wanted to ask.

Thanks

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
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***Anissa.Davis@fda.hhs.gov***



---

**From:** Kellie Kennon [mailto:kellie.kennon@asklepionpharm.com]
**Sent:** Friday, March 28, 2014 11:45 AM
**To:** Davis, Anissa
**Subject:** NDA 205750
**Importance:** High

Good morning Anissa,

This email is to inform you that the ISS datasets were successfully submitted to the application on March 26, 2014. Thank you for allowing those to be submitted this week.

Also, during our teleconference on March 14, 2014, the clinical reviewer requested that we confirm the diagnosis for subject 36. He indicated that upon review he had noted a discrepancy, but we are unable to locate any place whereby the subject is identified as having anything other than Zellwegers, which is one of the peroxisomal defects. Would it be possible to get additional information? We would very much like to correct any discrepancy, but have exhausted efforts to locate.

Many thanks,
Kellie

Kellie A. Kennon, BSN | Clinical Research Director |
**O**: +1 410.545.0494 ext 4 | **F**: +1 410.545.0584 | **M**: (b) (6) |
kellie.kennon@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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/s/

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ANISSA A DAVIS
03/31/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, March 14, 2014 9:46 AM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Pharmacology Information Request

**Importance:** High

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We acknowledge that you provided a validation report of LC-MS for atypical bile acids on February 26, 2014. However, according to your study report, the assay of atypical bile acids for Study CAC 001-01 was performed using FAB-MS. In your previous response to the Agency's IR, the in-study bioanalytical assay report for typical bile acids related to drug substance was submitted; however, the in-study assay report for atypical urinary bile acids was not submitted. Therefore we are requesting the information or further clarification.

1) In-study bioanalytical assay report submitted on February 21, 2014 in response to item 11 in the filing communication letter does not have information for quantitation of atypical urinary bile acids while concentrations of 3b, 7a-dihydroxy-d5 sulfate and other atypical bile acids in patients were provided in clinical study report. It is unclear how these concentrations were obtained since the FAB-MS assay was not validated for quantitation of atypical bile acids. Please clarify or provide an in-study bioanalytical assay report for quantitation of atypical urinary bile acids.

2) Provide tabulated Signal to Noise (S/N) ratio values over time that corresponds to the submitted individual mass spectra for each patient in Study CAC-91-10-10. Please indicate when the treatment was initiated and how long patients were on treatment at the time of each mass spectra. Relevant patient demography including but not limited to, age, gender, dose of cholic acid, and diagnosis of enzyme defect should also be included. In addition clarify how the S/N ratio was calculated as there are multiple peaks labeled in each mass spectra.

**Please submit your responses to me via email and officially to your application by April 4, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
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ANISSA A DAVIS
03/14/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, March 14, 2014 8:09 AM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Information Request

**Importance:** High

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We have the following clinical comments/information requests because we did not receive an adequate response to the clinical information requests annotated in the Filing Letter dated February 3, 2014:

1) Provide the FDA reviewable efficacy data (annotated summary tables with means, standard deviations, medians, minimum to maximum range, and number of patients) of liver serological markers (e.g., AST/ALT) and bilirubin test (direct, total, and indirect bilirubin) with the single enzyme defects and the peroxisomal disorders. Your responses provided on February 21, 2014 are considered inadequate because your original data is not annotated and summarized. The direct, total, and indirect bilirubin are not individually summarized. There is no analysis of your missing data.

2) Provide detailed narratives of the deaths for Patient IDs 0, 16, 103, 127, 143, 152, and 181. Failure to do so may lead to the potential safety concern of drug treatment-related deaths not being ruled-out.

**Please submit your responses to me via email and officially to your application by April 4, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
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/s/

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ANISSA A DAVIS
03/14/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Tuesday, March 11, 2014 4:00 PM
**To:** 'Gary Pasternack'
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750: FDA Responses to Remaining Applicant's Questions dated 3/7/14

**Importance:** High

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We also refer to your email correspondence dated March 7, 2014 requesting clarification regarding the Clinical/Statistical information requested dated March 5, 2014.

Questions provided by you on March 7, 2014 are in plain text. Responses provided by the FDA are in **bold text**.

**Questions and Responses**

1. Could the Agency please clarify how the population should be restricted in term of study medication regimen. Please refer to the study medication regimen table that was produced for the CSR. Here, our specific question is whether the Agency wishes only patients who received only cholic acid to be included in the requested analyses, or whether we can include all patients. If the data set is restricted to patients receiving cholic acid monotherapy only, the population reduces to 40 patients, which means that statistical power will also diminish.

   Please note that in Section 9.4.1 of the 91-10-10 Clinical Study Report, performed subgroup analyses comparing patients with cholic acid monotherapy to those who received URSO treatment at least once. (b) (4) The supporting data for this statement appear in Tables 17, 23, and 29 found in Section 9.4.1 of the 91-10-10 Clinical Study Report.

Distribution of Study Medication Regimens
Safety Population

| Regimen 1 | Regimen 2 | Regimen 3 | Number of Subjects | Percent of Safety Population |
|---|---|---|---|---|
| CHOLIC & CDA | | | 1 | 1 |
| CHOLIC & URSO | | | 5 | 6 |
| CHOLIC ONLY | | | 40 | 47 |
| CHOLIC ONLY | CDA ONLY | | 3 | 4 |
| CHOLIC ONLY | CHOLIC & URSO | | 4 | 5 |
| CHOLIC ONLY | CHOLIC AND CDA | | 1 | 1 |
| CHOLIC ONLY | DHA ONLY | | 3 | 4 |
| CHOLIC ONLY | DHA ONLY | DHA & CHOLIC | 1 | 1 |
| CHOLIC ONLY | URSO ONLY | | 16 | 19 |
| CHOLIC ONLY | URSO ONLY | CDA ONLY | 1 | 1 |
| CHOLIC ONLY | URSO ONLY | CHOLIC & URSO | 4 | 5 |
| URSO ONLY | CHOLIC & DHA | | 1 | 1 |

Abbreviations: CDA, chenodeoxycholic acid; URSO, ursodeoxycholic acid; DHA, decosahexaenic acid

**FDA Response:**
**There should be no restrictions in terms of study medication regimen. Please include all available patients.**

2. Could the Agency please clarify which liver function test and urinary bile acid data should be treated as and analyzed as continuous data: the ordinal scales (which we have for both), or the raw data (which we have for the liver function tests but not for the urinary bile acids)? The urinary bile acid data is based upon a categorical assessment of the urinary bile acid levels and is thus not a continuous variable.

**FDA Response:**
**We apologize for the confusion. The urinary bile acid data should be analyzed utilizing the ordinal scales as currently analyzed. The liver function tests to be analyzed as continuous data should be ALT and AST.**

3. Could the Agency please confirm that each patient's first observation should be considered the baseline observation for the ANCOVA?

**FDA Response:**
**For the cholic acid treatment group patients, baseline should signify the appropriate pre-treatment value, which depends on the specific type of analysis being conducted** (b) (4) **For the natural history patients, we agree that the first observation should be considered the baseline observation. Note that for all patients in these ANCOVA analyses, the appropriate post-treatment value depends on the specific type of analysis being conducted** (b) (4)

4. Could the Agency please confirm that no other independent variables should contribute to the model, i.e. that the model will be: post-treatment response = baseline response. If this is the case, as all patients received treatment, please clarify the statistical goal of the model?

**FDA Response:**
**The ANCOVA should be utilized for the requested continuous data analyses which will compare the cholic acid treatment group with the natural history cohort. Note that the natural history cohort would serve as the control group in these analyses. We are not requesting additional independent variables to be included in the model. However, for exploratory purposes, it is acceptable to include other independent variables if there are reasons to believe these variables may affect the treatment effect.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***

*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
*Silver Spring, Maryland*
*Use zip code **20903** if shipping via United States Postal Service (USPS)*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***



---

**From:** Davis, Anissa
**Sent:** Saturday, March 08, 2014 9:53 PM
**To:** 'Gary Pasternack'
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750

Hello Dr. Pasternack:
The answer to one of the following questions is below. The statistical reviewer will provide answers to the remaining questions.

**Applicant:** Could you also please let us know if our March 28 response would constitute a second major amendment?
**FDA Response:** No, there is only one major amendment allowed per review cycle. Therefore, your March 28 response will not constitute a second major amendment.

Thank you.

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
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***THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.***

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Friday, March 07, 2014 2:05 PM
**To:** Davis, Anissa
**Cc:** 'Kellie Kennon'
**Subject:** NDA 205750

Distribution of Study Medication Regimens
Safety Population

| Regimen 1 | Regimen 2 | Regimen 3 | Number of Subjects | Percent of Safety Population |
|---|---|---|---|---|
| CHOLIC & CDA | | | 1 | 1 |
| CHOLIC & URSO | | | 5 | 6 |
| CHOLIC ONLY | | | 40 | 47 |
| CHOLIC ONLY | CDA ONLY | | 3 | 4 |
| CHOLIC ONLY | CHOLIC & DHA | | 1 | 1 |
| CHOLIC ONLY | CHOLIC AND CDA | | 1 | 1 |
| CHOLIC ONLY | DHA ONLY | | 3 | 4 |
| CHOLIC ONLY | DHA ONLY | DHA & CHOLIC | 1 | 1 |
| CHOLIC ONLY | URSO ONLY | | 14 | 16 |
| CHOLIC ONLY | URSO ONLY | CDA ONLY | 1 | 1 |
| CHOLIC ONLY | URSO ONLY | CHOLIC & URSO | 4 | 5 |
| URSO ONLY | CHOLIC & DHA | | 1 | 1 |

Dear Anissa,

Thanks for your e-mail of March 5, 2014. As a first step in preparing our answers, we have reviewed the questions and requests with our statistician. The following questions have resulted. Given the March 28 deadline for our response, could we please ask for a response from the Reviewer no later than Tuesday, March 12, and preferably sooner? Could you also please let us know if our March 28 response would constitute a second major amendment? If it will constitute a second major amendment, would that in turn result in a further extension of the PDUFA date, or would the time required for evaluation of the second major amendment run concurrently with time required for the first major amendment, which is presumably under review by a separate group of Reviewers?

1. Could the Agency please clarify how the population should be restricted in term of study medication regimen. Please refer to the study medication regimen table that was produced for the CSR. Here, our specific question is whether the Agency wishes only patients who received only cholic acid to be included in the requested analyses, or whether we can include all patients. If the data set is restricted to patients receiving cholic acid monotherapy only, the population reduces to 40 patients, which means that statistical power will also diminish.

   Please note that in Section 9.4.1 of the 91-10-10 Clinical Study Report, performed subgroup analyses comparing patients with cholic acid monotherapy to those who received URSO treatment at least once. (b) (4) The supporting data for this statement appear in Tables 17, 23, and 29 found in Section 9.4.1 of the 91-10-10 Clinical Study Report.

Abbreviations: CDA, chenodeoxycholic acid; URSO, ursodeoxycholic acid; DHA, decosahexaenic acid

2. Could the Agency please clarify which liver function test and urinary bile acid data should be treated as and analyzed as continuous data: the ordinal scales (which we have for both), or the raw data (which we have for the liver function tests but not for the urinary bile acids). The urinary bile acid data is based upon a categorical assessment of the urinary bile acid levels and is thus not a continuous variable.

3. Could the Agency please confirm that each patient's first observation should be considered the baseline observation for the ANCOVA

4. Could the Agency please confirm that no other independent variables should contribute to the model, i.e. that the model will be: post-treatment response = baseline response. If this is the case, as all patients received treatment, please clarify the statistical goal of the model?

Once we have answers to these questions, we can begin the requested analyses.

As always, thanks VERY much.

Best
Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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/s/

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ANISSA A DAVIS
03/11/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Saturday, March 08, 2014 9:53 PM
**To:** 'Gary Pasternack'
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750

Hello Dr. Pasternack:
The answer to one of the following questions is below. The statistical reviewer will provide answers to the remaining questions.

**Applicant:** Could you also please let us know if our March 28 response would constitute a second major amendment?
**FDA Response:** No, there is only one major amendment allowed per review cycle. Therefore, your March 28 response will not constitute a second major amendment.

Thank you.

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
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*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***



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**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Friday, March 07, 2014 2:05 PM
**To:** Davis, Anissa
**Cc:** 'Kellie Kennon'
**Subject:** NDA 205750

Dear Anissa,

Thanks for your e-mail of March 5, 2014. As a first step in preparing our answers, we have reviewed the questions and requests with our statistician. The following questions have resulted. Given the March 28 deadline for our response, could we please ask for a response from the Reviewer no later than Tuesday, March 12, and preferably sooner? Could you also please let us know if our March 28 response would constitute a second major amendment? If it will constitute a second major amendment, would that in turn result in a further extension of the PDUFA date, or would the time required for evaluation of the second major amendment run concurrently with time required for the first major amendment, which is presumably under review by a separate group of Reviewers?



Distribution of Study Medication Regimens
Safety Population

| Regimen | Regimen 2 | Regimen 3 | Number of Subjects | Percent of Safety Population |
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| CHOLIC & CDA | | | 1 | 1 |
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| CHOLIC ONLY | | | 40 | 47 |
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| CHOLIC ONLY | CHOLIC & URSO | | 4 | 5 |
| CHOLIC ONLY | CHOLIC AND CDA | | 1 | 1 |
| CHOLIC ONLY | DHA ONLY | | 3 | 4 |
| CHOLIC ONLY | DHA ONLY | DHA & CHOLIC | 1 | 1 |

1. Could the Agency please clarify how the population should be restricted in term of study medication regimen. Please refer to the study medication regimen table that was produced for the CSR. Here, our specific question is whether the Agency wishes only patients who received only cholic acid to be included in the requested analyses, or whether we can include all patients. If the data set is restricted to patients receiving cholic acid monotherapy only, the population reduces to 40 patients, which means that statistical power will also diminish.



Please note that in Section 9.4.1 of the 91-10-10 Clinical Study Report, performed subgroup analyses comparing patients with cholic acid monotherapy to those who received URSO treatment at least once. (b) (4)

The supporting data for this statement appear in Tables 17, 23, and 29 found in Section 9.4.1 of the 91-10-10 Clinical Study Report.

Abbreviations: CDA, chenodeoxycholic acid; URSO, ursodeoxycholic acid; DHA, decosahexaenic acid

2. Could the Agency please clarify which liver function test and urinary bile acid data should be treated as and analyzed as continuous data: the ordinal scales (which we have for both), or the raw data (which we have for the liver function tests but not for the urinary bile acids). The urinary bile acid data is based upon a categorical assessment of the urinary bile acid levels and is thus not a continuous variable.

3. Could the Agency please confirm that each patient's first observation should be considered the baseline observation for the ANCOVA

4. Could the Agency please confirm that no other independent variables should contribute to the model, i.e. that the model will be: post-treatment response = baseline response. If this is the case, as all patients received treatment, please clarify the statistical goal of the model?

Once we have answers to these questions, we can begin the requested analyses.

As always, thanks VERY much.

Best
Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 107 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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/s/

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ANISSA A DAVIS
03/08/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Wednesday, March 05, 2014 6:13 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 (cholic acid): Clinical and Statistical Information Requests

Hello Dr. Pasternack:

**Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.**

**We are conducting a review of your submission and have the following information requests:**

**Clinical:**

1. Concerning Protocol 91-10-10 entitled "Investigations in the Pathogenesis of Liver Disease in Patients with Inborn Errors of Bile Acid Metabolism" and Protocol 92-8-19 entitled "Investigations of the potential benefit of Bile Acid Therapy for patients with Peroxisomal Disorders affecting Bile Acid Metabolism" we understand that the protocols were amended to allow for enrollment of subjects as outpatients and that they were not required to be seen at Cincinnati Children's Hospital Medical Center (CCHMC).

    a. Please provide a list of subjects that were seen at CCHMC and a list of subjects that were not seen at CCHMC.

    b. For those subjects that were not seen at CCHMC, please provide the location where the protocol required evaluations occurred and provide the location of the source documents for these evaluations.

**Statistical:**

Regarding Study CAC-91-10-10, please conduct the following additional analyses:

Repeat all efficacy analyses specified within your Statistical Analysis Plan (SAP) between those patients receiving cholic acid in Study CAC-91-10-10 and those who are part of your natural history cohort, and additional within-treatment group analyses using only those patients receiving cholic acid, for the following efficacy parameters:

- Urinary Bile acids by FAB-MS
- Liver Function Tests (Serum Transaminases - ALT and AST)
- Bilirubin
- Height and Weight

All these analyses should adhere to the following requests:

1. In addition to the categorical analyses presented for the urinary bile acids and liver function tests, analyze these two efficacy parameters as continuous data. This approach would be analogous to what has already been specified within your SAP for the analysis of the bilirubin and height/weight efficacy parameters.

When conducting these analyses using continuous data, we recommend utilizing an Analysis of Covariance (ANCOVA) model with the post-treatment measurement as the response/dependent variable, treatment (i.e., cholic acid or no treatment) as a factor, and the pre-treatment measurement as a covariate.

2. For the analyses between the Study CAC-91-10-10 cholic acid group and the natural history cohort, note that for the natural history/no-treatment patients the "pre-treatment" measurement could be their initially observed data point while the "post-treatment" measurement could be a designated data point (b) (4) after what was initially observed. In addition to the (b) (4) approaches already evaluated, you should also utilize other analysis approaches for these newly requested analyses which include (b) (4) median-to-median, mean-to-mean, and last-observation to last-observation. All analyses should be conducted using the ITT analysis population specified in your SAP.

3. All the aforementioned analyses should also be conducted by the following subgroups:
   - Bile Acid Disease Population (single enzyme defect, peroxisomal)
   - Gender (male, female)
   - Race (white, non-white, unknown)

**Please submit your responses to me via email and officially to your application by March 28, 2014.**

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
*White Oak Building 22 Room: 5378*
*10903 New Hampshire Avenue*
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*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

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ANISSA A DAVIS
03/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**REVIEW EXTENSION – MAJOR AMENDMENT**

Asklepion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, M.D., Ph.D.
Chief Executive Officer
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your November 21, 2013, New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

On January 24, 2014 and February 14, 2014, we received your major amendments to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is October 21, 2014.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017." If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by July 21, 2014. Furthermore, the new planned date for our internal mid-cycle review meeting is April 24, 2014.

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

*{See appended electronic signature page}*

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

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/s/

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BRIAN K STRONGIN
02/27/2014

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | Latest FDA Mark-Up of the CHOLBAM Labeling |
| **Date:** | Friday, February 27, 2015 3:38:56 PM |
| **Attachments:** | FDA package-insert-CHOLBAM word-version-Clean 2-27-15.docx<br>FDA package-insert-CHOLBAM word-version-red-lined 2-27-15.docx |

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I've attached the red-lined/strikeout and clean versions of the latest FDA mark-up of the package insert. Please let me know your changes, if possible, by the 3/5/15 teleconference. Thanks.

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/s/

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BRIAN K STRONGIN
02/27/2015

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Wednesday, February 26, 2014 5:26 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750- Regulatory Information Request-Label

**Importance:** High

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

Also refer to your submission dated February 21, 2014. We have the following regulatory request regarding the label:

- Please resubmit a clean word and pdf tracked-versions of the label without the column listed "Reference" as annotated in the previous submission. You can also visit *Implementing the PLR Content and Format Requirements* and *PLR Requirements for Prescribing Information* website (publically-available) for labeling resources or additional information that can assist you.

Please resubmit the requested labels officially to your application by March 21, 2014.

If you would like for me to review the label prior to the official submission, please let me know.

Thank you!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
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*White Oak Building 22 Room: 5378*
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***Anissa.Davis@fda.hhs.gov***

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/s/

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ANISSA A DAVIS
02/26/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Wednesday, February 26, 2014 4:51 PM
**To:** gary.pasternack@asklepionpharm.com; 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750: Clinical Information Request
**Attachments:** Keane_Perox_Bile Acid.pdf

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We refer you to the attached published article entitled, "Bile Acid Treatment Alters Hepatic Disease and Bile Acid Transport in Peroxisome-Deficient PEX2 Zellweger Mice" (Keane, MH, Overmars, H, Wikander, TM, Ferdinandusse, S, Duran, M, Wanders, RJ, and Faust, PL. Hepatology 45:982-997, 2007). Please conduct a literature review of this paper to determine if there is a potential safety issue of Cholbam treatment in patients with peroxisomal disorder. Also perform a literature search and provide a review of any other preclinical or clinical literature that may help to clarify this issue. Please submit this review to your NDA.

**Please submit your responses to me via email and officially to your application by April 30, 2014.**

Thank you!



*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
*Center for Drug Evaluation and Research*
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***Anissa.Davis@fda.hhs.gov***

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/s/

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ANISSA A DAVIS
02/26/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, February 21, 2014 11:28 AM
**To:** gary.pasternack@asklepionpharm.com; 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Cc:** Do, Phong
**Subject:** NDA 205750: DMEPA Information Request

**Importance:** High

**Hello Dr. Pasternack:**

**Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.**

(b) (4)

[redacted]

**Please submit the revised labeling officially to your application by March 21, 2014.**

**If you have further questions or need clarifications, please contact Phong Do, OSE Regulatory Project Manager, at 301-796-4795.**

Thank you!

Anissa

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, United States Public Health Service (USPHS)*
*Senior Regulatory Project Manager*
*Food and Drug Administration*
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/s/

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ANISSA A DAVIS
02/21/2014

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 205750

**PROPRIETARY NAME REQUEST**
**CONDITIONALLY ACCEPTABLE**

Asklepion Pharmaceuticals, LLC
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

ATTENTION: Kellie A. Kennon, BSN
Clinical Research Director

Dear Ms. Kennon:

Please refer to your New Drug Application (NDA) dated and received November 21, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Cholic Acid Capsules, 50 mg, 250 mg.

We also refer to your correspondence, dated and received December 3, 2013, requesting review of your proposed proprietary name, Cholbam. We have completed our review of the proposed proprietary name, Cholbam and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 3, 2013 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Phong Do, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4795. For any other information regarding this application, contact Anissa Davis, Regulatory Project Manager, in the Office of New Drugs at (301) 796-5016.

Sincerely,

*{See appended electronic signature page}*

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

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TODD D BRIDGES on behalf of KELLIE A TAYLOR
02/20/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**FILING COMMUNICATION -**
**FILING REVIEW ISSUES IDENTIFIED**

Askelpion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, M.D., Ph.D.
Chief Executive Officer
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for cholic acid capsules, 50 mg and 250 mg.

We also refer to your amendments dated December 3, 2013, December 4, 2013, December 19, 2013, December 20, 2013 and January 24, 2014.

During our filing review of your application, we identified the following potential review issues:

Clinical/Statistical:

1. Your proposed indication, (b) (4) is broad. (b) (4)

2. Three of the primary efficacy endpoints of the clinical trial submitted to support this NDA are surrogate biomarkers, not clinically meaningful endpoints and are unlikely to support regular approval. The adequacy of the data submitted to support the third endpoint of height/weight gain, which is a clinical benefit in these diseases, will be a significant review issue. As discussed with you in the meetings (dated January 25, 2010 and July 25, 2012) prior to your application, it is possible that urinary bile acids, and serum transaminases and bilirubin could support approval under Subpart H.

3. Your primary endpoints were not pre-specified. The (b) (4) methodology for urinary bile acid analysis, which was not discussed with the FDA prior to submission of the application, may not be an acceptable approach to defining responder criteria.

4. The historical control data were collected from the literature. These data may not be adequate to serve as qualified controls because the baseline characteristics of the historical control and the treatment groups may not be sufficiently comparable, or there may be inadequate information available to establish that they are sufficiently comparable.

5. The narratives of patients who died during Study CAC-91-10-10 do not provide sufficiently detailed clinical information for FDA review.

Clinical Pharmacology:

6. We note that the bioanalytical assay validation for urinary bile acids was done in a qualitative assessment not a quantitative assessment. (b) (4) This will be a review issue in the assessment of the suppression of the synthesis of atypical bile acids by cholic acid treatment.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

**We request that you submit the following information as soon as possible, or by February 21st, 2014 at the latest:**

Biopharmaceutics:

1. Provide solubility data for the drug substance covering the physiological pH range.

2. Provide data to support the discriminating ability of the selected dissolution method. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products (aberrant formulations) (b) (4) In addition, if available, submit data showing that the selected dissolution method is able to reject batches that are not bioequivalent.

3. Provide complete dissolution profile data (raw data and mean values) from the clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for all components of the proposed product.

4. To support the Level 2 drug product manufacturing site change, provide *in vitro* comparative dissolution data and f2 similarity values (n=12) for the drug product manufactured at the old and new site in three media: (b) (4) phosphate buffers pH (b) (4) and 6.8.

Clinical:

5. Provide efficacy data (summary tables and original data) of liver serological markers (e.g., AST/ALT/GGT), bilirubin test (direct, total, and indirect bilirubin) and PT/INR in patients with a single enzyme defect.

6. Provide clinical details for the narratives of the Patient IDs 0, 16, 103, 127, 143, 152, and 181.

7. On page 20 of your clinical overview you state that you prepared a revised clinical study report to address the EMA comments. Please provide a copy of the EMA comments and clarify how you revised the study report to address these comments.

8. Provide the "coding dictionary" consisting of a list of all investigator verbatim terms and the preferred terms to which they were mapped.

Statistical:

9. For Study CAC-91-10-10, provide separate subgroup efficacy analyses by gender and by race for the primary efficacy variables. For the subgroup efficacy analysis by race, there should be three subgroups analyzed: Whites, Non-Whites, and Unknown.

Nonclinical:

10. Identify the reference articles, including the location of these publications in the NDA, which provide supporting evidence for the mechanism of action described in subsection 12.1 of your draft labeling. If you have not provided information to support the proposed mechanism of action, please do so.

Clinical Pharmacology:

11. Provide the in-study bioanalytical assay report for urinary bile acids and serum bile acids presented in Table 3, Listing 8 and 11 in Study CAC-001-01.

**During our preliminary review of your submitted labeling, we have identified the following labeling format issues. We request that you resubmit labeling that addresses these issues by February 17, 2014. The resubmitted labeling will be used for further labeling discussions.**

1. The length of Highlight (HL) must be one-half page or less (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted

in a previous submission (e.g., the application being reviewed is an efficacy supplement). The HL is greater than one-half page.

2. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. There was no white space before “ADVERSE REACTIONS” heading.

3. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic. The first bullet under "USE IN SPECIFIC POPULATIONS" does not have reference.

4. The revision date must be at the end of HL, and should be bolded and right justified (e.g., “Revised: 9/2013”). The revision date is missing.

5. In the Table of Contents (TOC), all section headings must be bolded and should be in UPPER CASE. Entire section is in blue font; therefore, it was unable to determine if bolded are not.

6. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)]. Entire section is in blue font. Therefore, it is unable to determine if bolded are not.

7. The section and subsection headings in the TOC must match the section and subsection headings in the FPI. Subsection 12.2 Pharmacodynamics, located in the FPI, is not annotated in TOC.

8. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.” The statement "*Sections or subsections omitted from the full prescribing information are not listed" is not annotated as required.

9. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in italics and enclosed within brackets. For example, “[see Warnings and Precautions (5.2)]” or “[see Warnings and Precautions (5.2)]”. The cross-references in the FPI are annotated with section number only.

10. When clinical trials adverse reactions data are included (typically in the "Clinical Trials Experience" subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

    "Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice."

    The above statement is not annotated.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

**PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

*{See appended electronic signature page}*

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

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ANDREW E MULBERG
02/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**METHODS VALIDATION**
**MATERIALS RECEIVED**

Asklepion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, MD, PhD
729 E. Pratt St.
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CHOLBAM™ (cholic acid) capsules, 50 mg and 250 mg and to our December 20, 2013, letter requesting sample materials for methods validation testing.

We acknowledge receipt on January 31, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

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MICHAEL L TREHY
01/31/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Wednesday, January 29, 2014 11:06 AM
**To:** 'Gary Pasternack'
**Cc:** 'Kellie Kennon'; McKnight, Rebecca
**Subject:** RE: IR Question for NDA 205750
**Attachments:** Bioanalytical Method Validation.pdf

Hello Dr. Pasternack:

Per "Guidance for Industry: Bioanalytical Method Validation" (attached), the applicant should submit chromatograms from 20% of serially selected subjects to support the approval of pivotal bioequivalence studies. The reviewer noticed that not enough chromatograms were included in the report of human subject samples analysis. Please include more chromatograms in the report.

*HAPPY NEW YEAR!!!!*

***Anissa***

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, USPHS Commissioned Corps*
*Regulatory Project Manager*
*Food and Drug Administration/Center for Drug Evaluation and Research*
*Division of Gastroenterology/Inborn Errors Products*
*Office of Drug Evaluation III*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***



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**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Tuesday, January 28, 2014 12:50 PM
**To:** Davis, Anissa
**Cc:** 'Kellie Kennon'; McKnight, Rebecca
**Subject:** RE: IR Question for NDA 205750

Cmdr Davis,

We are presently arranging for uploading and hyperlinking of the attached documents, which I believe are what the Reviewer has requested. Please confirm. Please let me know if the Reviewer wishes us to upload the original data files as well (which are too numerous and bulky to e-mail).

We regret the omission and any inconvenience that it might have caused.

Thanks,

Best,
Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



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**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Tuesday, January 28, 2014 9:32 AM
**To:** 'Gary Pasternack MD PhD'
**Cc:** Kellie Kennon; McKnight, Rebecca
**Subject:** RE: IR Question for NDA 205750

Sir,
Per the reviewer, "The analytical report of the BE study submitted by the applicant was not complete. Usually, the analytical report consists of the method validation and the report of human subject sample analysis. The latter is missing.
The report of human subject sample analysis refers to how the PK data were acquired using the validated bioanalytical method, which includes the raw data and are different from the reported PK data."

*HAPPY NEW YEAR!!!!*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, USPHS Commissioned Corps*
*Regulatory Project Manager*
*Food and Drug Administration/Center for Drug Evaluation and Research*
*Division of Gastroenterology/Inborn Errors Products*
*Office of Drug Evaluation III*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*

***Anissa.Davis@fda.hhs.gov***



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**From:** Gary Pasternack MD PhD [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Tuesday, January 28, 2014 9:26 AM
**To:** Davis, Anissa
**Cc:** Kellie Kennon; McKnight, Rebecca
**Subject:** Re: IR Question for NDA 205750

The pharmacokinetic study is already part of the submission and can be found under M5331 along with all appendices. Please confirm that this resolves the query.

Thanks
Gary Pasternack

Gary R Pasternack, MD, PhD
Chief Executive Officer
Asklepion Pharmaceuticals LLC
729 E Pratt St, Suite 360
Baltimore, MD 21202

Sent from my iPad

On Jan 28, 2014, at 9:20 AM, "Davis, Anissa" <Anissa.Davis@fda.hhs.gov> wrote:

> The reviewer is referring to the Bioequivalence study.
>
> *HAPPY NEW YEAR!!!!*
>
> ***Anissa***
>
> ***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
> *CDR, USPHS Commissioned Corps*
> *Regulatory Project Manager*
> *Food and Drug Administration/Center for Drug Evaluation and Research*
> *Division of Gastroenterology/Inborn Errors Products*
> *Office of Drug Evaluation III*
> *(301) 796-5016(office)*
> *(301) 796-9904 (fax)*
> ***Anissa.Davis@fda.hhs.gov***
>
> 

***If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.***

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**From:** Gary Pasternack MD PhD [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Tuesday, January 28, 2014 8:49 AM
**To:** Davis, Anissa
**Cc:** Kellie Kennon
**Subject:** Re: IR Question for NDA 205750

THANKS

Gary R Pasternack, MD, PhD
Chief Executive Officer
Asklepion Pharmaceuticals LLC
729 E Pratt St, Suite 360
Baltimore, MD 21202

Sent from my iPad

On Jan 28, 2014, at 8:47 AM, "Davis, Anissa" <Anissa.Davis@fda.hhs.gov> wrote:

> Sir,
> I will reach out to the reviewer and inquire. I will let you know.
>
> *HAPPY NEW YEAR!!!!*
>
> ***Anissa***
>
> ***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
> *CDR, USPHS Commissioned Corps*
> *Regulatory Project Manager*
> *Food and Drug Administration/Center for Drug Evaluation and Research*
> *Division of Gastroenterology/Inborn Errors Products*
> *Office of Drug Evaluation III*
> *(301) 796-5016(office)*
> *(301) 796-9904 (fax)*
> ***Anissa.Davis@fda.hhs.gov***
>
> 
>
> ---
>
> **From:** Gary Pasternack MD PhD [mailto:gary.pasternack@asklepionpharm.com]
> **Sent:** Tuesday, January 28, 2014 8:43 AM

**To:** Davis, Anissa
**Cc:** Kellie Kennon
**Subject:** Fwd: IR Question for NDA 205750

Cmdr Davis -

I just received the question below from FDA and asked for clarification as to precisely what was being requested. I immediately received an automatic response from Rebecca McKnight stating that she would be out of the office today.

Given the short time frame for response, could you kindly help clarify precisely what is being requested so that we can be responsive?

Thanks
Gary Pasternack

Gary R Pasternack, MD, PhD
Chief Executive Officer
Asklepion Pharmaceuticals LLC
729 E Pratt St, Suite 360
Baltimore, MD 21202

Sent from my iPad

Begin forwarded message:

> **From:** Gary Pasternack MD PhD <gary.pasternack@asklepionpharm.com>
> **Date:** January 28, 2014 at 8:37:58 AM EST
> **To:** "McKnight, Rebecca" <Rebecca.McKnight@fda.hhs.gov>
> **Cc:** Kellie Kennon <kellie.kennon@asklepionpharm.com>
> **Subject: Re: IR Question for NDA 205750**
>
> Dear Dr McKnight,
>
> I just want to make sure that we are referring to the same study. Are you referring to the pharmacokinetic study? Just want to be certain that we are referring to the same study.
>
> Thanks
> Gary Pasternack
>
> Gary R Pasternack, MD, PhD
> Chief Executive Officer
> Asklepion Pharmaceuticals LLC
> 729 E Pratt St, Suite 360
> Baltimore, MD 21202
>
> Sent from my iPad

On Jan 28, 2014, at 8:33 AM, "McKnight, Rebecca" <Rebecca.McKnight@fda.hhs.gov> wrote:

Dear Dr. Pasternack,

We are reviewing NDA 205750, and have the following IR question:

- Provide the bioanalytical study report by January 31, 2014.

If you have any questions, please contact me. Please send a .pdf copy of your amendment to me via email as well as making a formal submission to the NDA.

Thank you,

Rebecca McKnight
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
CDER-ONDQA
301-796-1765

25 pages of the FDA “Guidance for Industry: Bioanalytical Method Validation” have been withheld. They can be found online at http://www.fda.gov/downloads/Drugs/Guidances/ucm070107.pdf

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/s/

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ANISSA A DAVIS
01/29/2014

## McKnight, Rebecca

**From:** McKnight, Rebecca
**Sent:** Tuesday, January 28, 2014 8:33 AM
**To:** 'gary.pasternack@asklepionpharm.com'
**Subject:** IR Question for NDA 205750

Dear Dr. Pasternack,

We are reviewing NDA 205750, and have the following IR question:

- Provide the bioanalytical study report by January 31, 2014.

If you have any questions, please contact me. Please send a .pdf copy of your amendment to me via email as well as making a formal submission to the NDA.

Thank you,

Rebecca McKnight
Regulatory Health Project Manager
Division of New Drug Quality Assessment III
CDER-ONDQA
301-796-1765

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/s/

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REBECCA A MCKNIGHT
01/28/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**PRIORITY REVIEW DESIGNATION**

Asklepion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, M.D., Ph.D.
Chief Executive Officer
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We also refer to your submissions dated December 3, 2013, December 4, 2013, December 19, 2013, and December 20, 2013.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. This application is also subject to the provisions of "the Program" under the Prescription Drug User Fee Act (PDUFA) V (refer to: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm . Therefore, the user fee goal date is July 21, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 21, 2014. In addition, the planned date for our internal mid-cycle review meeting is February 27, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

While conducting our filing review, we identified potential review issues and will communicate them to you on or before February 3, 2014.

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

*{See appended electronic signature page}*

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Director
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

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ANDREW E MULBERG
01/19/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, January 17, 2014 8:15 PM
**To:** 'Gary Pasternack'
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

**Importance:** High

Dr. Pasternack:

Please see the Agency's responses in red regarding NDA 205750.

1 We are working on the mass spectra underlying the primary analysis, which involves approximately 175 individual spectra. De-identification, annotation and calculation of the signal to noise ratio takes approximately 15 minutes per spectrum, with additional time required for processing into a PDF and document handling – the average is 20 minutes per spectrum. Overall, this is anticipated to take several people 60 to 70 hours to complete. The tabulation, grouping, and incorporation into a submission will take an additional several days. Our timetable is further compromised by the holiday on Monday. Would it be acceptable to the Agency to submit the first group of spectra on Friday, January 24, 2104?

FDA Response: This is acceptable

2. In addition to the spectra underlying the primary analysis, there are approximately 500 additional individual spectra. These will take an additional 170 to 180 hours to process in accordance with the Agency's request. Our ability to meet this request is compromised by circumstances beyond our control. (b) (4) [redacted] I believe that we would be able to furnish organized, grouped, de-identified, un-annotated spectra to the Agency on or before the requested February 3, 2014 due date since this does not require Dr. We would then commit to furnishing annotated, hyperlinked spectra by the end of February. Given the circumstances, is this acceptable to the Agency?

FDA Response: Your inability to provide the requested data is a refuse to file issue; however, we are trying to be flexible and will file the NDA and allow you to send the data in as soon as possible. Please be aware that it is possible that the responses to items #1 and #3 will trigger a major amendment and an extension. If you cannot provide the response to item #2 until the end of February, then it is most likely that this response will trigger an extension. **Please submit the annotated hyperlinked spectra by February 21, 2014.**

3. We have found that the short timeframe and the holiday on January 20, 2013 compromises the ability of our CRO to publish the revised tables, the more legible figures for the validation report, and the answers to the additional questions by the deadline of January 21. Would it be acceptable to the Agency to combine the mass spectra from the primary analysis and the foregoing items into a single submission on Friday, January 24, 2014?

FDA Response: This is acceptable

HAPPY NEW YEAR!!!!

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, USPHS Commissioned Corps*
*Regulatory Project Manager*
*Food and Drug Administration/Center for Drug Evaluation and Research*
*Division of Gastroenterology/Inborn Errors Products*
*Office of Drug Evaluation III*
*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***



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**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Friday, January 17, 2014 3:11 PM
**To:** Davis, Anissa
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR
**Importance:** High

Anissa,

Thank you very much for the Agency responses which were very constructive and helpful. As I indicated in a previous e-mail, I would be in a better position to respond to the question of timing once I had a better understanding of the scope of the work.

In that spirit, I'd like to clarify the submission timetable with you, and would like to discuss a couple of obstacles that we have:

1. We are working on the mass spectra underlying the primary analysis, which involves approximately 175 individual spectra. De-identification, annotation and calculation of the signal to noise ratio takes approximately 15 minutes per spectrum, with additional time required for processing into a PDF and document handling – the average is 20 minutes per spectrum. Overall, this is anticipated to take several people 60 to 70 hours to complete. The tabulation, grouping, and incorporation into a submission will take an additional several days. Our timetable is further compromised by the holiday on Monday. Would it be acceptable to the Agency to submit the first group of spectra on Friday, January 24, 2104?

2. In addition to the spectra underlying the primary analysis, there are approximately 500 additional individual spectra. These will take an additional 170 to 180 hours to process in accordance with the Agency's request. Our ability to meet this request is compromised by circumstances beyond our control. (b) (4) [redacted] I believe that we would be able to furnish organized, grouped, de-identified, un-annotated spectra to the Agency on or before the requested February 3, 2014 due date since this does not require Dr. We would

then commit to furnishing annotated, hyperlinked spectra by the end of February. Given the circumstances, is this acceptable to the Agency?

3. We have found that the short timeframe and the holiday on January 20, 2013 compromises the ability of our CRO to publish the revised tables, the more legible figures for the validation report, and the answers to the additional questions by the deadline of January 21. Would it be acceptable to the Agency to combine the mass spectra from the primary analysis and the foregoing items into a single submission on Friday, January 24, 2014?

Thanks for your kind consideration of these requests.

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Friday, January 17, 2014 8:30 AM
**To:** 'Gary Pasternack'
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR
**Importance:** High

Dr. Pasternack:
Please see the Agency's responses in red to your questions below regarding the Clinpharm Information Request (IR) dated January 15, 2014 for NDA 205750. Also, please refer back to the IR and submit all that has been requested.

1. We plan to submit the tables for CAC-001-0 with units, etc. as requested as attachments to the letter detailing our responses. As of this writing, we foresee no problems in submitting this by 21 January. Will this be acceptable?

   **FDA Response: Acceptable**

2. We need further clarification regarding the request for the spectra. Firstly, is this a request for all spectra, i.e. all time points, or for a subset consisting of a before, during, and after for each patient? Further, we are not clear on what "after" means since cholic acid therapy, once instituted, is lifelong and there really isn't an "after". Could you please clarify. The spectra underlying the analyses consisted of single pre-Rx and single post-Rx (post-Rx means on therapy) spectra. Are these the spectra that should be submitted?

   The answer to this question is very important in terms of timing. For some patients, there are large numbers of spectra. In order to comply with the request, the staff at CCHMC along with sponsor personnel will need to pull each spectrum, copy it, and then hand-annotate it to point out the abnormal ions corresponding to the abnormal bile acids, and finally calculate the signal to noise ratio and annotate the spectra. If this request pertains to all spectra, the final number may well exceed 300. The short timeframe to accomplish this, even for a subset, is further complicated by [a] the holiday on Monday – Cincinnati Children's Hospital personnel will be

unavailable, and [b] (b) (4) we are dependent upon him to oversee the work on the spectra and the annotations.

**FDA Response: The word "after" was meant to be spectra at the time of efficacy assessment.**

**We request all spectra. We note that you analyzed urinary bile acid data in different ways (b) (4) It is unclear to us what that means in terms of the changes in urinary bile acid profile over time. Therefore we request that you submit all spectra organized in a chronological manner by individual patient grouped by primary diagnosis. Please identify which data was used for statistical analysis.**

**In the meantime, it will be acceptable that you submit the mass spectra underlying the primary analysis first (for example see Table 2.7.3-6) followed by additional spectra. Please organize the spectra by patient grouped by primary diagnosis.**

**Given the urinary bile acid data was analyzed (b) (4) we assume the signal to noise ratio has been computed for other mass spectra which were not used for statistical analysis if multiple mass spectra were available. If such information exists in a separate data file, it will be acceptable that you submit a separate file for the signal to noise ratio for each spectra as far as the data can be easily linked back to corresponding spectra.**

3. When we submit the spectra, could you please clarify the Agency's expectations for hyperlinking, etc.? If extensive hyperlinking is required, could we submit spectra in two stages – first providing the spectra, and then following up with a hyperlinked submission, which would take longer?

**FDA Response: Yes, hyperlinking is required to assist in reviewing the information. Yes, you can submit spectra in the two stages you suggested.**

4. We believe we can respond as outlined above to all questions other than the request for spectra by the deadline.

**FDA Response: We need the data (at least spectra without hyperlinking) By February 3, 2014.**

*HAPPY NEW YEAR!!!!*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, USPHS Commissioned Corps*
*Regulatory Project Manager*
*Food and Drug Administration/Center for Drug Evaluation and Research*
*Division of Gastroenterology/Inborn Errors Products*
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*(301) 796-5016(office)*
*(301) 796-9904 (fax)*
***Anissa.Davis@fda.hhs.gov***

***of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0069. Thank you.***

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Thursday, January 16, 2014 11:12 AM
**To:** Davis, Anissa
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR
**Importance:** High

Anissa,

Thanks very much for your response. We've just finished a conference call to organize our responses. Here are a few more questions that have resulted.

1. We plan to submit the tables for CAC-001-0 with units, etc. as requested as attachments to the letter detailing our responses. As of this writing, we foresee no problems in submitting this by 21 January. Will this be acceptable?

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4. We believe we can respond as outlined above to all questions other than the request for spectra by the deadline.

Please get back to me with answers as soon as you can – particularly the questions regarding the spectra.

Thanks
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Thursday, January 16, 2014 10:00 AM
**To:** 'Gary Pasternack'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

Thanks for your voicemail message and email below. I will need to ask the clinical pharmacology reviewer if this would be acceptable. I will update you later today.

Thanks

*HAPPY NEW YEAR!!!!*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
*CDR, USPHS Commissioned Corps*
*Regulatory Project Manager*
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*(301) 796-5016(office)*
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***Anissa.Davis@fda.hhs.gov***



---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Wednesday, January 15, 2014 6:31 PM
**To:** Davis, Anissa
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR
**Importance:** High

Anissa,

Do we have any flexibility with the submission date? I believe that we can get many of the requests in by the 21st , but some are quite labor-intensive and require sending people to the clinical site to pull the records. Specifically, the following request

- For studies CAC 001-01 and CAC 91-10-10, please submit the mass spectra for individual patients for urine bile acids before, during and after treatment. For each spectra, we recommend that atypical bile acids be identified and the signal-to-noise ratio be documented.

Involves pulling, copying, annotating, and organizing hundreds of records, then incorporating them into an appendix. That is a tall order for effectively three working days and little time subsequently for publication as an e-submission. I will have some further questions on formatting and hyperlinking expectations from our CRO shortly. For now, the main question is whether we can extend the submission date – if not for the entire set of requests, at least for this item. Please note that we are very happy to comply with the request – all that we ask is that we be given a reasonable amount of time to accomplish it. We are setting up a conference call tomorrow to organize this project. I will have a much better feel for the amount of time required thereafter.

Thanks
Gary Pasternack

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**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

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729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Wednesday, January 15, 2014 5:40 PM
**To:** 'Gary Pasternack'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

Thanks Dr. Pasternack. It would probably be best to ask your questions via email. This way, I can send to the reviewer to respond.

*HAPPY NEW YEAR!!!!*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
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***Anissa.Davis@fda.hhs.gov***



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**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Wednesday, January 15, 2014 5:36 PM
**To:** Davis, Anissa
**Cc:** "Kellie Kennon"
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

Anissa,

We are initiating work on this immediately. I may need to call you tomorrow for some clarifications.

Best
Gary

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

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---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Wednesday, January 15, 2014 5:32 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 Cholbam (cholic acid): ClinPharm IR

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We are conducting a review of the clinical pharmacology section of your submission and have the following information requests:

- In the report of Study CAC-001-0, the units for tabulated values and footnotes are missing in all Tables. We recommend that Tables updated with units and relevant footnotes be submitted.

- The chromatograms presented in the LC-MS validation report-serum-complete (16.1.10) is not legible e.g. Figures 1 and 2 in pages 19-20. We recommend resubmission of legible chromatograms.

- For studies CAC 001-01 and CAC 91-10-10, please submit the mass spectra for individual patients for urine bile acids before, during and after treatment. For each spectra, we recommend that atypical bile acids be identified and the signal-to-noise ratio be documented.

- Please clarify whether urine samples collected for bile acids were analyzed by FAB-MS on the same day or different days.

- Please submit the normal range of atypical bile acids in healthy subjects if such information is available.

**Please submit your responses officially to your application and to me via email (exact copies of official submission) by January 21, 2014.**

Thank you!

HAPPY NEW YEAR!!!!

Anissa

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

---

ANISSA A DAVIS
01/17/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Friday, January 17, 2014 8:30 AM
**To:** 'Gary Pasternack'
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

**Importance:** High

Dr. Pasternack:
Please see the Agency's responses in red to your questions below regarding the Clinpharm Information Request (IR) dated January 15, 2014 for NDA 205750. Also, please refer back to the IR and submit all that has been requested.

1. We plan to submit the tables for CAC-001-0 with units, etc. as requested as attachments to the letter detailing our responses. As of this writing, we foresee no problems in submitting this by 21 January. Will this be acceptable?

   **FDA Response: Acceptable**

2. We need further clarification regarding the request for the spectra. Firstly, is this a request for all spectra, i.e. all time points, or for a subset consisting of a before, during, and after for each patient? Further, we are not clear on what "after" means since cholic acid therapy, once instituted, is lifelong and there really isn't an "after". Could you please clarify. The spectra underlying the analyses consisted of single pre-Rx and single post-Rx (post-Rx means on therapy) spectra. Are these the spectra that should be submitted?

   The answer to this question is very important in terms of timing. For some patients, there are large numbers of spectra. In order to comply with the request, the staff at CCHMC along with sponsor personnel will need to pull each spectrum, copy it, and then hand-annotate it to point out the abnormal ions corresponding to the abnormal bile acids, and finally calculate the signal to noise ratio and annotate the spectra. If this request pertains to all spectra, the final number may well exceed 300. The short timeframe to accomplish this, even for a subset, is further complicated by [a] the holiday on Monday – Cincinnati Children's Hospital personnel will be unavailable, and [b] (b) (4) we are dependent upon him to oversee the work on the spectra and the annotations.

   **FDA Response: The word "after" was meant to be spectra at the time of efficacy assessment.**

   **We request all spectra. We note that you analyzed urinary bile acid data in different ways (b) (4) It is unclear to us what that means in terms of the changes in urinary bile acid profile over time. Therefore we request that you submit all spectra organized in a chronological manner by individual patient grouped by primary diagnosis. Please identify which data was used for statistical analysis.**

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3. When we submit the spectra, could you please clarify the Agency's expectations for hyperlinking, etc.? If extensive hyperlinking is required, could we submit spectra in two stages – first providing the spectra, and then following up with a hyperlinked submission, which would take longer?

   **FDA Response: Yes, hyperlinking is required to assist in reviewing the information. Yes, you can submit spectra in the two stages you suggested.**

4. We believe we can respond as outlined above to all questions other than the request for spectra by the deadline.

   **FDA Response: We need the data (at least spectra without hyperlinking) By February 3, 2014.**

*HAPPY NEW YEAR!!!!*

***Anissa***

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
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**Sent:** Thursday, January 16, 2014 11:12 AM
**To:** Davis, Anissa
**Cc:** 'Kellie Kennon'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR
**Importance:** High

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Thanks
Gary

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gary.pasternack@asklepionpharm.com

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729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Thursday, January 16, 2014 10:00 AM
**To:** 'Gary Pasternack'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

Thanks for your voicemail message and email below. I will need to ask the clinical pharmacology reviewer if this would be acceptable. I will update you later today.

Thanks

*HAPPY NEW YEAR!!!!*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
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**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Wednesday, January 15, 2014 5:40 PM
**To:** 'Gary Pasternack'
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

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**Sent:** Wednesday, January 15, 2014 5:36 PM
**To:** Davis, Anissa
**Cc:** "Kellie Kennon"
**Subject:** RE: NDA 205750 Cholbam (cholic acid): ClinPharm IR

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Best
Gary

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---

**From:** Davis, Anissa [mailto:Anissa.Davis@fda.hhs.gov]
**Sent:** Wednesday, January 15, 2014 5:32 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 Cholbam (cholic acid): ClinPharm IR

Hello Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

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- Please submit the normal range of atypical bile acids in healthy subjects if such information is available.

**Please submit your responses officially to your application and to me via email (exact copies of official submission) by January 21, 2014.**

Thank you!

HAPPY NEW YEAR!!!!

Anissa

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
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*Regulatory Project Manager*
*Food and Drug Administration/Center for Drug Evaluation and Research*
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*(301) 796-5016(office)*
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***Anissa.Davis@fda.hhs.gov***

---

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

---

ANISSA A DAVIS
01/17/2014

## Davis, Anissa

**From:** Davis, Anissa
**Sent:** Wednesday, January 15, 2014 5:32 PM
**To:** gary.pasternack@asklepionpharm.com
**Cc:** 'Kellie Kennon' (kellie.kennon@asklepionpharm.com)
**Subject:** NDA 205750 Cholbam (cholic acid): ClinPharm IR

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**Please submit your responses officially to your application and to me via email (exact copies of official submission) by January 21, 2014.**

Thank you!

HAPPY NEW YEAR!!!!

Anissa

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

---

ANISSA A DAVIS
01/15/2014

**Davis, Anissa**

| | |
|---|---|
| **From:** | Davis, Anissa |
| **Sent:** | Monday, January 06, 2014 4:03 PM |
| **To:** | gary.pasternack@asklepionpharm.com; 'Kellie Kennon' (kellie.kennon@asklepionpharm.com) |
| **Subject:** | NDA 205750 (cholic acid): USAN Request |
| **Importance:** | High |

Hello Dr. Pasternack:

We have received your New Drug Application (NDA) submitted under section pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

In May of 2005, you were informed that "cholic acid" was not in the USAN dictionary and you needed to apply to USAN for approval to use "cholic acid" as the established name (see finalized meeting minutes dated June 28, 2005). You apparently have not done so; cholic acid is still not in the USAN dictionary. **Please apply for the USAN as soon as possible, and inform me via email when this has been done.**

Thank you.

*HAPPY NEW YEAR!!!!*

*Anissa*

***Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.***
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***Anissa.Davis@fda.hhs.gov***

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/s/

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ANISSA A DAVIS
01/06/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**REQUEST FOR METHODS VALIDATION MATERIALS**

Asklepion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, MD, Ph.D.
729 E. Pratt St.
Baltimore, MD 21202
FAX: (410) 545-0584

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CHOLBAM™ (cholic acid) capsules, 50 mg and 250 mg.

We will be performing methods validation studies on CHOLBAM™ (cholic acid) capsules, 50 mg and 250 mg, as described in NDA 205750.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method, current version**

Drug Substance: Assay and Related Impurities (HPLC)
Drug Product: Identification, Assay and Related Substances of Cholic Acid Capsules by HPLC

**Samples and Reference Standards**

2 x 2 g Cholic acid reference standard
10 g Cholic acid drug substance
100 CHOLBAM™ (cholic acid) capsules, 50 mg
100 CHOLBAM™ (cholic acid) capsules, 250 mg
100 mg [redacted] (b) (4) reference standard
100 mg [redacted] (b) (4) reference standard
100 mg [redacted] (b) (4) reference standard

**Equipment**

1 [redacted] (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

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MICHAEL L TREHY
12/20/2013

# MEMORANDUM OF TELECONFERENCE

**Teleconference Date**: July 29, 2013

**Application Number**: IND 45470
**Product Name:** cholic acid
**Sponsor/Applicant Name:** Asklepion Pharmaceuticals

**Subject**: Reminder of PDUFA V requirements

**FDA Participants**
Lara Dimick, CDTL
Wen-Yi Gao, MO
David Joseph, Nonclinical TL
Marie Kowblansky, Pharmaceutical Lead, ONDQA
Insook Kim, Clinical Pharmacology Reviewer
Jessica Benjamin, RPM

**Sponsor/Applicant Participants**
Gary Pasternack, CEO, Asklepion
Kellie Kennon, Clinical Research Director, Asklepion
Ken Roberts, Business Operations Manager, Asklepion
(b) (4) Regulatory Consultant
(b) (4) Regulatory Consultant
(b) (4) CMC Consultant
(b) (4)

## 1.0 BACKGROUND:

The purpose of this teleconference with the sponsor was to discuss the PDUFA V Program requirements for a complete application since the Pre-NDA meeting for IND 45470 was before PDUFA V went into effect. The Pre-NDA industry meeting for this application was held on January 25, 2010. The sponsor plans to submit their NME NDA in August 2013.

## 2.0 DISCUSSION:

During this teleconference, the sponsor was reminded that their NDA, when submitted, would fall under the PDUFA V program and that a complete application is required at the time of submission. Under the PDUFA V program, a comprehensive list of CMC and study sites also needs to be included or referenced in the application. The FDA suggested that the sponsor review the PDUFA V goals letter for a full description of NDA requirements (link to be sent after meeting).

Dr. Joseph reiterated the nonclinical requirements that were stated in the response to Question 6 in the January 2010 meeting minutes. Asklepion stated that they have PK data in adult volunteers to address FDA's concern.

Asklepion explained that they had a change in manufacturing sites (b) (4) to Bourgoin, France. FDA stated that the NDA would need to contain 3 months of stability data from the new manufacturing facility in France. FDA requested Asklepion forward an outline of what will be submitted in Module 3, including a comparison of the (b) (4) and Bourgoin data, linking the two manufacturing facilities and comparative analysis that would be provided in the NDA.

## 3.0 ACTION ITEMS

Asklepion will submit the requested information and FDA will respond in 1-2 days on whether or not the sponsor's CMC plan is acceptable.

Additional information attached to the memo of teleconference:
1. Background information that was emailed to the FDA prior to the teleconference
1. FDA's final determination on CMC components

| | |
|---|---|
| **From:** | Gary Pasternack |
| **To:** | Benjamin, Jessica |
| **Cc:** | (b) (4) Kellie Kennon; (b) (4) Ken Roberts; (b) (4) |
| **Subject:** | IND 45,470 NDA Filing - Teleconference July 29, 2013 12:30 pm |
| **Date:** | Friday, July 26, 2013 2:31:04 PM |

Dear Jessica,

Thank you very much for arranging the teleconference on such short notice. We are submitting this brief background information along with the questions we have regarding the CMC section of our NDA for discussion during the telephone conference.

As will be explained in detail in the NDA, cholic acid is (b) (4) performed by (b) (4) The subsequent manufacture of the cholic acid drug product, (b) (4) occurred at a plant (b) (4) that is owned by Patheon. The commercial scale registration/stability batches of cholic acid drug product that are described in the NDA (b) (4) has been transferred to a facility in Bourgoin, France that is also owned by Patheon. The NDA will also contain information on two manufacturing process feasibility batches from the facility in France. These development lots were part of the technical transfer of the manufacturing process between the two facilities and were used to gather process information prior to manufacture of the conformance batches. Information on the conformance batches, which we intend to commercialize, will become available during the review of the NDA.

As you know, cholic acid has been designated as an orphan product. Moreover, it is currently in short supply, and we anticipate that FDA may grant priority review to this NDA. Accordingly, consistent with CPG Sec. 490.100 ("Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval") and FDA guidance (notably "Questions and Answers on Current Good Manufacturing Practices- Production and Process Controls" and "Draft Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics") Asklepion plans to submit an NDA that does not contain information on conformance batches of drug product that are currently being manufactured at the Bourgoin, France facility.

This leads to the following issues for discussion:

1) Asklepion plans to file the NDA with an information package that contains the registration/ stability batches manufactured (b) (4) (Section 3.2.P.5.4) and development information gathered from the manufacturing process feasibility lots manufactured at the proposed commercial site in Bourgoin, France(Section 3.2.P.2.3). While data from conformance lots produced during Process Validation will be available at the pre-approval inspection, Asklepion does not plan to include this information in the initial submission of the NDA. Does the Agency concur that the proposed data package is sufficient to allow FDA review?

2) To inform your inspection activities, we wanted to note that the facility in Bourgoin, France has never been inspected by FDA, but has undergone numerous successful regulatory inspections by EMA and others.

I will put this e-mail into letter form and will additionally file three copies to the IND.

Once again, thanks for agreeing to this conference call.

Sincerely,
Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

**From:** Benjamin, Jessica
**To:** Gary Pasternack
**Cc:** Benjamin, Jessica
**Subject:** RE: RESPONSE TO CMC QUESTIONS
**Date:** Friday, August 09, 2013 1:00:33 PM

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Dr. Pasternack,

On reviewing the information that you plan to submit, we have the following comments:

1. You do not plan to submit any stability data for product manufactured at the proposed commercial site (Patheon-France). You only plan to submit stability data for the registration batches manufactured in Patheon-(b) (4) Since the manufacturing process involves some small differences between the two sites, and you will be imprinting the commercial batches (while the registration batches were not imprinted), we will require that at the time of NDA submission you provide at least one month of stability data for the two feasibility batches manufactured at the Patheon-France site and that you provide at least 3 months of long term- and accelerated stability data for these feasibility batches no later than 30 days after submission of the NDA.

2. We note that you do not plan to submit executed batch records for batches manufactured at Patheon-France. You will need to submit both master and executed batch records for registration batches manufactured at Patheon (b) (4) and for the feasibility batches manufactured at Patheon-France.

3. At the time of submission, you will need to provide a statement that all sites involved in the manufacture of this product, including the Patheon-France site are ready for inspection

The above comments are based on our evaluation of the type of information you intend to submit. The actual information that you submit in support of your NDA will be evaluated at the time of NDA review.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*



---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Wednesday, August 07, 2013 12:16 PM
**To:** Benjamin, Jessica
**Cc:** (b) (4) Ken Roberts; Kellie Kennon; (b) (4)
**Subject:** RE: RESPONSE TO CMC QUESTIONS

Jessica,

This row designating not for human use was inserted in the table to clarify the batch use. Since these

lots were prepared specifically to gather data for process feasibility /technical transfer between Patheon (b) (4) and Patheon-France, Asklepion wanted to emphasize that they will not be used in ongoing clinical trials nor should they be considered launch stock once the NDA is approved.

I hope that this helps clarify the issue.

Best
Gary Pasternack

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA



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**From:** Benjamin, Jessica [mailto:Jessica.Benjamin@fda.hhs.gov]
**Sent:** Wednesday, August 7, 2013 11:29 AM
**To:** Gary Pasternack
**Cc:** Benjamin, Jessica
**Subject:** RE: RESPONSE TO CMC QUESTIONS

Dr. Pasternack,

In response to the information below, please explain why you refer to “feasibility batches” as “not for human use”?

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*

---

**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Monday, August 05, 2013 12:07 PM
**To:** Benjamin, Jessica
**Cc:** (b) (4) Kellie Kennon; (b) (4) Ken Roberts; (b) (4)
**Subject:** RESPONSE TO CMC QUESTIONS

Jessica,

Below are the responses to your questions. I have attached a revised memo incorporating the changes.

Please acknowledge receipt.

Thanks

Best
Gary

1. Besides being at different sites, what are the differences in the manufacture of the registration batches and the feasibility batches?

Table 4 of the CMC document was included to help clarify this information. In preparation of the response to this question, Asklepion realized that the column headings were not as clear as they could have been. The column previously entitled "technical transfer" lots is now entitled "Manufacturing Process Feasibility (Technical Transfer) Lots. A revised table is shown below and included in the attachment to this email. The table shows that the manufacturing process between the registration stability lots and the manufacturing process feasibility lots is the same with a few exceptions.

(b) (4)

**Table 4: Comparison of Registration Stability Lots, Manufacturing Feasibility Lots and Process Validation Lots of Cholic Acid Capsules**

| Parameter | Registration Stability Lots | Manufacturing Process Feasibility (Technical Transfer) Lots | Process Validation Lots |
|---|---|---|---|
| Location | Patheon (b) (4) | Patheon – France, Bourgoin-Jallieu | Patheon – France, Bourgoin-Jallieu |
| Purpose | Full scale manufacture, Clinical supply, registration stability lots;<br><br>For clinical human use | Manufacturing process feasibility, collection of data on process parameters<br><br>Not for human use | Process Validation, Site specific stability, clinical supplies, commercial stock (once approved)<br>For human use |

| Manufacturing Status | Manufactured October 2009 and January 2010 | Manufactured June 2013 | Scheduled for July and August 2013 |
|---|---|---|---|
| Scale | 50 mg: (b) (4)<br>250 mg (b) (4) | 50 mg: (b) (4)<br>250 mg: (b) (4) | 50 mg (b) (4)<br>250 mg: (b) (4) |
| Number of Lots | 50 mg: 3<br>250 mg: 3 | 50 mg: 1<br>250 mg: 1 | 50 mg: 2<br>250 mg: 2 |
| Process Parameters | (b) (4) | | |
| Key Equipment: SUPAC Class / Subclass | (b) (4) | | |
| Component (b) (4) Used | (b) (4) | | |

2. Why do you refer to the batches as feasibility batches, rather than pilot batches?

(b) (4)

The term manufacturing process feasibility was meant to be a descriptor for lots manufactured as part of the technical transfer of the process from Patheon (b) (4) to Patheon-France.

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
O: +1 410.545.0494 ext 7 | F: +1 866.339.3910 | M: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

APPEARS THIS WAY ON ORIGINAL

**From:** Benjamin, Jessica
**To:** Gary Pasternack
**Cc:** Benjamin, Jessica
**Subject:** RE: CMC Questions - Response to FDA
**Date:** Wednesday, August 28, 2013 2:43:30 PM

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Dr. Pasternack,

At this time we must repeat our advice regarding the schedule for submitting stability data for product manufactured at the new site. At least one month of accelerated- and long-term stability data will be required at the time of submission, with additional two-month and three-month data being provided no later than 30 days after original submission of the NDA. The three month data will give us significant additional information on which to determine the comparability of product from the two manufacturing sites and on which to base expiration dating.

Regards,
Jessica

Jessica M. Benjamin, MPH
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of New Drugs III
Center for Drug Evaluation and Research
301-796-3924 *office*
301-796-9904 *fax*



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**From:** Gary Pasternack [mailto:gary.pasternack@asklepionpharm.com]
**Sent:** Wednesday, August 21, 2013 4:52 AM
**To:** Benjamin, Jessica
**Cc:** (b) (4) Ken Roberts; Kellie Kennon
**Subject:** CMC Questions - Response to FDA

Dear Jessica,

We first wish to respond to your comments and clarify the manufacturing process. (b) (4) We also want to note that while we appreciate your flexibility, the "feasibility batches" were discarded and were not put on stability and so it will not be possible to provide stability data on those batches at any time.

We also wish to note that the NDA will contain stability information of at least three years for the registration batches manufactured at Patheon (b) (4) It will also contain a forced degradation study of the cholic acid drug substance under extreme conditions. Together, these results demonstrate

that the cholic acid drug substance and drug product are incredibly stable. We have every reason to believe that the Patheon-France product will be just as stable, but we understand your need to have confidence in that prediction.

Therefore, Asklepion would like to propose the following:

1) We will delay submitting the NDA until we can provide one-month of stability data for the first two commercial scale process validation batches from the Patheon-France site (one batch for the 50 mg strength capsule, and one batch for the 250 mg strength capsule). No later than 30 days after submission of the NDA, we will provide 60-day stability on both batches, plus 30-day stability on the next two commercial scale process validation batches (again, one batch for the 50 mg strength capsule, and one batch for the 250 mg strength capsule). We can update the NDA with 3-month (or later) stability data if the Division requests it after that point.

2) Given the delay in submission, we will be able to submit master and executed batch records for the first two process validation batches manufactured at Patheon-France. We will also submit both master and executed batch records for registration batches manufactured at Patheon (b) (4) This should obviate the need for master and executed batch records for the feasibility batches manufactured at Patheon-France.

3) At the time of submission, we will provide a statement that all sites involved in the manufacture of this product, including the Patheon-France site are ready for inspection.

We hope this proposal is acceptable. If so, we will be able to submit the NDA in the first half of October.

Best regards,

Gary R. Pasternack, MD, PhD | Chief Executive Officer |
**O**: +1 410.545.0494 ext 7 | **F**: +1 866.339.3910 | **M**: (b) (6) |
gary.pasternack@asklepionpharm.com

ASKLEPION PHARMACEUTICALS, LLC.
729 East Pratt Street, Suite 360, Baltimore, Maryland 21202, USA

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/s/

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JESSICA M BENJAMIN
12/02/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**NDA ACKNOWLEDGMENT**

Askelpion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, M.D., Ph.D.
Chief Executive Officer
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

Dear Dr. Pasternack:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: cholic acid capsules, 50 mg and 250 mg

Date of Application: November 21, 2013

Date of Receipt: November 21, 2013

Our Reference Number: NDA 205750

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 20, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call CDR Anissa Davis-Williams, Regulatory Project Manager, at (301) 796-5016.

Sincerely,

*{See appended electronic signature page}*

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

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ANISSA A DAVIS
11/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 45,470

**MEETING MINUTES**

Asklepion Pharmaceuticals, LLC
Attention: Theresa Shalaby, RN, BSN, CCRP
Clinical Research Director
5200 Maryland Way, Suite 204
Brentwood, TN 37207

Dear Ms. Shalaby:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Cholic Acid, 250 mg Capsules.

We also refer to the meeting between representatives of your firm and the FDA on January 25, 2010. The purpose of the meeting was to discuss your planned bridging study and clinical data in preparation for a future NDA submission.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2259.

Sincerely,

*{See appended electronic signature page}*

Chantal Phillips, M.S.H.S.
CDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

**Meeting Type:** B
**Meeting Category:** Pre-NDA

**Meeting Date and Time:** January 25, 2010; 12:00 – 1:00 pm EST
**Meeting Location:** FDA, White Oak

**Application Number:** IND 45,470
**Product Name:** Cholic Acid, 250 mg Capsules
**Indication:** (b) (4)

**Sponsor/Applicant Name:** Asklepion Pharmaceuticals, LLC

**Meeting Chair:** Dr. Lynne Yao
**Meeting Recorder:** Chantal Phillips

## FDA ATTENDEES

Division of Gastroenterology Products
Donna Griebel, M.D., Director
Helen Sile, M.D., Medical Reviewer
Lynne Yao, M.D., Acting Medical Team Leader
David Joseph, Ph.D., Pharmacology Reviewer
Ke Zhang, Ph.D., Pharmacology Reviewer
Chantal Phillips, CDR, M.S.H.S., Regulatory Project Manager

Pre-Marketing Assessment Division II
Marie Kowblansky, Ph.D., Pharmaceutical Assessment Lead

Division of Biometrics III
Mike Welch, Ph.D, Statistical Team Leader

Office of Clinical Pharmacology
Insook Kim, Ph.D., Reviewer

Office of Orphan Products Development
Jeff Fritsch, R.Ph., Regulatory Review Officer
Louise-Marie Gillis, Pharmacy Student

## SPONSOR ATTENDEES

Gary R. Pasternack, M.D., President & CEO, Asklepion

James E. Heubi, M.D., Director, General Clinical Research Center, Professor of Pediatrics, Pediatric Gastroenterology, Hepatology, and Nutrition, Cincinnati Children's Hospital Medical Center

Kenneth D. R. Setchell, PhD., Professor, Department of Pathology, Cincinnati Children's Hospital Medical Center

(b) (4)

(b) (4) (Consultant)

Theresa M. Shalaby RN, BSN, CCRP, Clinical Research Director, Asklepion

(b) (4) Regulatory Consultant

## 1.0 BACKGROUND

Asklepion Pharmaceuticals, LLC had a Type C Meeting with the Agency on September 25, 2007, to discuss the content of their proposed NDA submission for Cholic Acid. Asklepion submitted another Meeting Request on September 17, 2009, to discuss their planned bridging study and clinical data for their planned NDA submission and the discussion below represents that meeting request.

## 2. DISCUSSION

In response to questions in the December 21, 2009, background package, the following responses were given. The format provides the firm's questions in italics followed by FDA responses in bold lettering. Questions, responses, and additional comments are indicated with headings.

**Introductory Comments:**

**Generally, adequate and well-controlled trials with prospectively collected data are required to demonstrate efficacy and safety of a drug product. However, the Agency may consider reviewing efficacy data retrospectively collected and analyzed if adequate justification for the use of this type of study is provided.**

**You have provided retrospectively collected data on the effect of cholic acid on a number of conditions related to defect in bile acid synthesis. However, some of these conditions do not appear to respond to cholic acid. The data you have submitted suggest that efficacy may be limited to only 3β-HSD and $\Delta^4$-3-oxosteroid 5 β-reductase deficiency patients. You should carefully select the conditions that are most likely to respond to cholic acid and provide efficacy data to support specific indications for use.**

**You must also provide data to support the effectiveness of cholic acid on a clinically meaningful endpoint (e.g., decreased requirement for liver transplant or overall survival), or a surrogate endpoint that would be reasonably likely to predict clinical benefit (e.g., normalization of liver transaminases, normalization of serum bilirubin, or normalization of atypical bile acid metabolites in serum and urine after treatment with cholic acid). Additionally, supportive secondary efficacy evaluation should be conducted to demonstrate clinically relevant benefits such as improvement in growth using height and weight and BMI data; or improvement in absorption of fat soluble vitamins based on discontinuation of fat soluble vitamin supplementation. These data may be retrospectively collected; however, these data must be compared to a carefully selected control population. Therefore, identification of a historical control group based on the natural history data collected in the specific enzyme defect you have studied is important to establish as an adequate comparator. Additionally, a methodology for analyses of the relevant efficacy parameters should be provided along with plans for handling missing data, conflicting results, and poor documentation. Patients that have been lost to follow-up (page 48 of 52, volume 1 of 4) should be addressed and accounted for in the efficacy analyses.**

**If the currently available retrospectively collected data are unconvincing or uninterpretable due to lack of standardized data collection and analyses, a clinical trial using newly diagnosed bile acid synthesis deficiency patients (specifically 3β-HSD and $\Delta^4$-3-oxosteroid 5 β-reductase deficiency patients as the target population) would likely be required to demonstrate efficacy and safety of cholic acid. Based on the known pathophysiology of inborn errors of bile acid synthesis, it may be reasonable to evaluate changes in atypical bile acid metabolites in serum and urine along with normalization of liver transaminases, or normalization of serum bilirubin (total and direct bilirubin). It appears that liver transaminases can take 3-4 months to normalize and have been observed to take up to 10 months to normalize, but a normalization of total bilirubin may occur as quickly as 4 weeks in some patients. Again, an approval under 21 CFR 314 Subpart H, could be considered based on improvement in these potential surrogate markers. You must also provide justification regarding the selection of these endpoints as surrogate markers (i.e., reasonably likely based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit). Also, your clinical trial should be designed to study patients to capture improvement in all chosen endpoints.**

**You may also choose to demonstrate efficacy based on normalization in atypical bile acid metabolites in serum and urine. If so, you should consider using a method such as gas/liquid chromatography and mass spectrometry (G/LC-MS) to not only identify the peaks but also to provide quantification of atypical bile acids in urine and serum. Your proposal and description of changes in FAB-MS is limited by its inability to provide quantification as provided in the patients' data in Appendix G of volume 1 of 4. The atypical bile acid peaks that will be monitored using the G/LC-MS method pre and post cholic acid treatment should be identified and prespecified in your clinical trial protocol. These prespecified peaks identified on the G/LC-MS analyses should then be followed during and post cholic acid treatment for normalization as compared to healthy age matched controls. Justification should be provided for the peaks selected on the G/LC-MS. The handling of G/LC-MS peak variability as it relates to inter and intra patient variability, diet, diurnal, and day to day variability should be discussed in the methodology for analyses of the primary endpoint.**

**Additional Discussion:**

**The Agency recognizes the limited number of patients that are available for study in the U.S. (approximately 25 patients), and emphasized that the Sponsor should focus their clinical development program on a subset of clearly defined conditions that provide the most substantial evidence of efficacy. The Agency reiterated that the Sponsor focus on a population that have similar clinical characteristics and disease course. Clearly defining a patient population for study would aid in the identification of primary and secondary outcomes that are clinically relevant and could potentially be used to demonstrate evidence of effectiveness of cholic acid for these specific enzymatic defects.**

**The Agency also clarified that the Sponsor may consider use of retrospectively collected data that might have the potential to support the efficacy of cholic acid. The Agency**

**recommended that these data may be evaluated to identify efficacy endpoints focusing on the 2 enzymatic defects (3β-HSD and $\Delta^4$-3-oxosteroid 5 β-reductase deficiency) The Sponsor stated that much of the data collected for these specific conditions belong to former collaborators located in Europe. At the present time, the Sponsor does not believe that the European data will be available for analysis. Therefore, the quality and quantity of data are limited to data collected in U.S. patients. The Agency recommended that continued efforts should be made for the Sponsor to obtain agreements to use data from European patients, if possible.**

**Additionally, the Agency noted that relevant clinical data presented in published literature (Gonzales et al, 2009) should be considered as potential efficacy measures. The Agency also discussed the methodology for the evaluation of bile acid metabolites. There was no agreement reached during the meeting regarding the appropriate methodology for the evaluation of bile acid metabolites. However, additional comments regarding the methodology are included below (see Additional comments section.)**

Question 1.

*Will the study as detailed in the protocol be adequate to bridge from the previous study drug to the To Be Marketed product?*

**FDA Response:**

**Bridging studies are only needed to support a change in formulation once efficacy and safety is established in a prior formulation. However, in order to use changes in transaminases or atypical bile acid profiles for an acceptable bridging study, you will need to demonstrate that these endpoints are acceptable surrogate markers (please see the introductory comments). You should also justify the criteria to establish the equivalency based on the proposed PD endpoints once they are accepted as surrogate endpoints. In addition, a relative bioavailability based on plasma PK should be assessed between the to-be-marketed formulation and the clinical formulation(s).**

Question 2.

*Does the Division agree with the study design detailed in the protocol in regard to:*

*(a) clinical endpoints?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

*(b) study sample size?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

*(c) inclusion/exclusion criteria?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

*(d) treatment/observation periods?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

*(e) efficacy/safety assessments (labs, etc)?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

*(f) statistical analysis plan?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

Question 3.

*Does the Division have any additional comments regarding the protocol?*

**FDA Response:**

**No.**

Question 4.

*Does the Division agree that the clinical data and analyses of the data are adequate to support submission of an NDA for use of cholic acid capsules 250 mg* (b) (4) *?*

**FDA Response:**

**No, we do not agree. Please see introductory comments. Again, we remind that if you plan to use an historical control group as the comparator, the historical control group should be carefully matched with your treatment group. The characteristics of the historical control group that are used to match your treatment group should be based on clinically relevant characteristics that are derived from natural history studies. This historical control group may be derived from natural history data that you have collected in patients with specific defects in cholic acid synthesis and/or from literature sources. However, you have not provided specific details regarding the historical control group that you are planning to study. For example, it appears that your historical controls had a presumed diagnosis of inborn errors of bile acid synthesis, and the diagnosis was not confirmed in all cases. Thus, if a clear diagnosis is not established in the control group, the effectiveness of cholic acid in the treatment group will be difficult to interpret.**

*(a) If not, what additional statistical analysis would be needed?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

*(b) If not, what additional clinical data would be required?*

**FDA Response:**

**Please see introductory comments. It is premature to answer this question.**

Question 5.

*If the data do not seem adequate to demonstrate sufficient clinical benefit to support approval, would the data seem adequate to support approval under 21 CFR 314, Subpart H, that is, on the basis of an endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity?*

**FDA Response:**

**Please see introductory comments. Again, we recommend that you establish a study design with a carefully chosen study population, clear efficacy endpoints, and a valid measurement of efficacy endpoints that will evaluate the effect of cholic acid. If you choose to study a relevant clinical endpoint then regular approval may be considered. If, however, you choose an endpoint based on a surrogate marker (i.e., an endpoint that is reasonably likely based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit) then approval under 21 CFR 314 Subpart H may be considered.**

Question 6.

*Since cholic acid is an endogenous compound normally produced in the body, will any additional toxicology data be necessary?*

**FDA Response:**

**In general, we agree that nonclinical studies may not be needed to support approval. However, this will depend on whether the proposed dose levels are expected to produce a total body content of cholic acid (i.e., endogenous cholic acid + exogenous cholic acid) that exceeds the normal body content of cholic acid in the pediatric population. You must provide the following information to address this issue: the amount (endogenous pool) and synthetic rate of cholic acid in normal neonates, infants, and children, and any available information on the quantity of endogenous cholic acid in infants with inborn errors of bile acid synthesis. If this issue is not addressed or if the requested information does not provide assurance of safety, then a toxicity study of at least 3 months duration in a nonrodent species (neonates) will be needed.**

**You should reduce the impurity limits to comply with the qualification threshold in ICH guidance Q3B(R2), or provide information to assure the safety of the impurities at the proposed limits.**

**Additional Comments:**

1. **If you decide to conduct a clinical trial in the newly diagnosed patients, consider collecting additional clinical laboratory data such as total cholesterol levels, fat soluble vitamin levels (i.e.. vitamin A, vitamin E, vitamin K, and 25-hydroxy-vitamin D) and calcium levels at appropriate intervals to provide adequate safety monitoring.**

2. **Provide genotype information for all patients.**

3. **When available, initial and follow-up liver biopsy results should be provided.**

4. **Documentation of clinical findings including jaundice, fatty stools, hepatomegaly, splenomegaly, areflexia should be provided as part of the patients' physical examinations.**

5. **The proposed methodology (i.e., GS-MS or LC-MS) selected for monitoring atypical bile acids must be adequately justified, and information regarding the proposed methodology should include the following:**
   - **The specific marker/peak that will be evaluated**
   - **Justification for the evaluation of the specific marker/peak in a specific biologic sample (i.e., urine versus serum samples).**

- **The relationship of the specific marker/peak to a meaningful clinical outcome**
- **Adequate validation for the bioanalytical assay method used to evaluate each bile acid species**

6. **We recommend that plasma pharmacokinetics of cholic acid be characterized with the to-be-marketed formulation.**

## 3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

## 4.0 ACTION ITEMS

None.

## 5.0 ATTACHMENTS AND HANDOUTS

None.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| IND-45470 | GI-1 | ASKLEPION PHARMACEUTICALS LLC | CHOLIC ACID |

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/s/

CHANTAL N PHILLIPS
02/19/2010

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,470

R&R Registrations
Attention: Ronald Leonardi, Ph.D.
President
P.O. Box 262069
San Diego, CA 92196-2069

Dear Dr. Leonardi:

Please refer to the Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cholic Acid.

We also refer to the Chemistry, Manufacturing, and Controls pre-NDA meeting between representatives of your firm and the FDA on May 31, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9333.

Sincerely,

*{See appended electronic signature page}*

Monika Houstoun, Pharm.D.
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

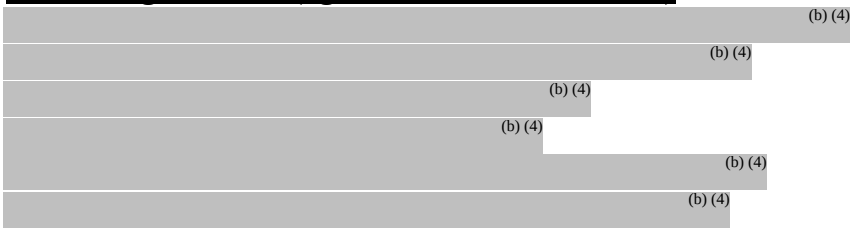
# Memorandum of Meeting Minutes

**Meeting Date:** May 31, 2005
**Meeting Time:** 10:30-12:00 p.m.
**Meeting Location:** Conference Room K, Parklawn Building, Rockville, MD

**Application Number:** IND 45,470
**Drug Name:** Cholic Acid
**Type of Meeting:** Type B
**Meeting Chair:** Liang Zhou, Ph.D.
**Meeting Recorder:** Monika Houstoun, Pharm.D.

**BETWEEN:**

**R & R Registrations (agent for Dr. James Heubi)**




Mr. Tomas Gonzalez, R & R Registrations
Dr. Ronald G. Leonardi, R & R Registrations

**AND**

Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180
Brian E. Harvey, M.D., Ph.D., Director
Joyce Korvick, M.D., M.P.H., Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader
Liang Zhou, Ph.D., Chemistry Team Leader
Ramesh Raghavachari, Ph.D., Chemistry Reviewer
Monika Houstoun, Pharm.D., Regulatory Project Manager

**Office of New Drug Chemistry II, HFD-820**
Eric Duffy, Ph.D., Director

**PURPOSE:**

To discuss the Chemistry, Manufacturing, and Controls for Cholic Acid and requirements for NDA submission.

**BACKGROUND:**

On June 5, 1994, Dr. James E. Heubi submitted IND 45,470 for Cholic Acid (b) (4)

On August 6, 2004, R & R Registrations submitted a meeting request and background package for a Type B, pre-NDA meeting for Cholic Acid. Enclosed in the package was a cross reference letter from Dr. James E. Heubi, dated July 27, 2004, for R & R Registrations to utilize data gathered under IND 45,470 for a pre-NDA meeting (b) (4) On September 16, 2004, Dr. James E. Heubi submitted a letter requesting that Ronald Leonardi of R & R Registrations act as his agent for all matters related to the pre-NDA meeting.

On October 25, 2004, R & R Registrations met with the Agency to discuss the drug development program for Cholic Acid and requirements for NDA submission.

On March 31, 2005, R & R Registrations submitted a request for a Chemistry, Manufacturing, and Controls pre-NDA meeting. On April 14, 2005, R & R Registrations submitted a background package for the meeting. On May 12, 2005, R & R Registrations submitted additional background meeting information.

On May 26, 2005, responses to the questions were faxed to R & R Registrations.

DISCUSSION:

Responses to the questions posed by the sponsor.

QUESTIONS FOR FDA:

*The Agency previously asked us to supply* (b) (4)

We have provided this information in the full CMC submission (CTD format) to support our meeting. (b) (4)

**Q1. Does the Agency feel that the characterization of the molecule is sufficient?**

**FDA Response:**

**Provide full characterization of the drug substance (Cholic Acid)** (b) (4) **If synthetic or semi-synthetic Cholic Acid is commercially available, provide comparative test data to demonstrate** (b) (4) **your product. Provide appropriate scientific literature references. (refer to 1987-Drug Substance guideline)**

**Q2. Does the Agency agree with our position (b) (4)?**

**FDA Response:**

**Proposed impurities (b) (4) appear to be acceptable.**

- **We recommend that you provide data to show (b) (4) impurities by using contemporary analytical test methods.**
- **Provide data to demonstrate that the impurities that interfere with analytical detection systems are identified and characterized.**
- **Refer to ICH Q3A and Q3B for qualification of impurities.**
- **Provide data in tabular form which identifies batches of drug substance used in preclinical and clinical studies. Also, provide characterization data to include impurity profiles and identity of impurities where possible for all drug substance batches.**

*The Agency has requested us to clarify (b) (4)*

We have provided an explanation in the documentation.

**Q3. Does the Agency agree with this interpretation?**

**FDA Response:**

**Provide confirmatory analytical data which demonstrates removal of these impurities in the NDA submission or by cross reference to DMF.**

*Further, the Agency requested us to establish test in the drug substance specifications for the above noted components.*

We would like not to have drug substance specifications for these components, but to validate the removal or level of these components (b) (4) This data will be presented in the DMF.

**Q4. Does the Agency agree with this concept?**

**FDA Response:**

**Submission of the above information in the DMF seems acceptable.**

*The Agency requested (b) (4) the specifications for related substances based on manufacturing batch data.*

Since we have limited test data information, we have only produced three batches of [redacted] Cholic Acid, identified as “Pharmaceutical Grade”, we feel we do not have sufficient experience [redacted] However, it is possible to set a limit of [redacted] for unknown impurity for now and to reevaluate it when we have more data.

**Q5. Does the Agency agree with this strategy?**

**FDA Response:**

**The above strategy appears to be acceptable.**

***The sponsor proposes 3 batches.***

> *The Agency requested [redacted] the specifications for residual solvent [redacted] based on manufacturing batch test data.*

Again, considering the limited manufacturing experience with the [redacted] product we suggest a preliminary limit of [redacted] ppm and to reevaluate it as we produce more batches and obtain more data.

**Q6. Does the Agency agree?**

**Agency Response:**

**This approach is acceptable. Define the number of batches that you will use for reevaluation of the specification.**

> *The Agency has requested that related substances in the Drug Substance be determined using a quantitative method (e.g. HPLC) in addition to TLC.*
>
> *Further, the Agency also requested that specification [redacted] of the Drug Product be determined using a quantitative method.*

Although the TLC method has been validated verifying detection limits and specificity, we are working on an HPLC assay, with an RI detection system, which could be utilized for both the Drug Substance and Drug Product. At our meeting we will present the available data and describe to the Agency what system we are developing to meet their request.

**Q7. In the eventuality that the development of this assay becomes a formidable task and all clinical work is completed and we are prepared to file an NDA, would the Agency allow us to file the NDA with our validated TLC assay until we can fully develop and validate a new HPLC assay?**

**FDA Response:**

**No. You need to develop the HPLC method before NDA submission.**

> *The Agency asked us to develop a working reference standard for the Drug Substance.*

We have developed a working standard (b) (4) of the current production of Cholic acid and have described it in our full submission.

**Q8. Does the Agency agree with this process and reference standard?**

**FDA Response:**

**You should consider a (b) (4) reference standard. Provide complete (b) (4) characterization data for the reference standard.**
**Refer to ICH Q6A, 1987 Drug Substance Guideline.**

> *The Agency requested that we discuss the (b) (4) issue with them at a CMC meeting.*

We have documented in our full submission (b) (4)

Additional documentation will be provided (b) (4)

**Q9. Does the Agency feel that this information is sufficient to support the claim (b) (4)?**

**FDA Response:**

**Provide documentation (scientific literature, process validation and other studies) to support your claim (b) (4)**

**Additional Comments:**

**'Cholic Acid' is not in the USAN 2005 dictionary. Please apply for USAN approval for the use of Cholic acid as the name.**

**Minutes Preparer:** _____
Monika Houstoun, Pharm.D.
Regulatory Project Manager

**Chair Concurrence:** _____
Liang Zhou, Ph.D.
Chemistry Team Leader

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/s/

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Liang Zhou

6/28/05 12:26:32 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 45,470

R&R Registrations
Attention: Ronald Leonardi, Ph.D.
President
P.O. Box 262069
San Diego, CA 92196-2069

Dear Dr. Leonardi:

Please refer to the Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cholic Acid.

We also refer to the pre-NDA meeting between representatives of your firm and the FDA on October 25, 2004.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-9333.

Sincerely,

*{See appended electronic signature page}*

Monika Houstoun, Pharm.D.
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

# Memorandum of Meeting Minutes

**Meeting Date:** October 25, 2004
**Meeting Time:** 11:00-12:30 p.m.
**Meeting Location:** Potomac Conference Room, Parklawn Building, Rockville, MD

**Application Number:** IND 45,470
**Drug Name:** Cholic Acid
**Type of Meeting:** Type B
**Meeting Chair:** Hugo Gallo-Torres, M.D., Ph.D.
**Meeting Recorder:** Monika Houstoun, Pharm.D.

**BETWEEN:**

**R & R Registrations (agent for Dr. James Heubi)**
Dr. Kenneth D. R. Setchell, Professor of Pediatrics, (b) (4)
Cincinnati Children's Hospital Medical Center
(b) (4)
(b) (4)
(b) (4)
(b) (4)
Dr. Ronald G. Leonardi, President, R & R Registrations

**AND**

**Division of Gastrointestinal and Coagulation Drug Products (DGCDP), HFD-180**
Hugo Gallo-Torres, M.D., Ph.D., Medical Team Leader
Jasti Choudary, Ph.D., Supervisory Pharmacologist
Ke Zhang, Ph.D., Pharmacologist
Ramesh Raghavachari, Ph.D., Chemistry Reviewer
Monika Houstoun, Pharm.D., Regulatory Project Manager

**Office of Clinical Pharmacology and Biopharmaceutics (OCPB), HFD-870**
Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

**Division of Biometrics II (HFD-715)**
Stella Grosser, Ph.D., Statistical Team Leader

**Office of Orphan Products Development (OOPD), HFD-035**
John McCormick, M.D., Deputy Director
Brad Glasscock, Pharm.D., Reviewing Pharmacist

**PURPOSE:**

To discuss the drug development program for Cholic Acid and requirements for NDA submission.

**BACKGROUND:**

On June 5, 1994, Dr. James E. Heubi submitted IND 45,470 for Cholic Acid (b) (4)

On August 6, 2004, R & R Registrations submitted a meeting request and background package for a Type B, pre-NDA meeting for Cholic Acid. Enclosed in the package was a cross reference letter from Dr. James E. Heubi, dated July 27, 2004, for R & R Registrations to utilize data gathered under IND 45,470 for a pre-NDA meeting (b) (4) On September 16, 2004, Dr. James E. Heubi submitted a letter requesting that Ronald Leonardi of R & R Registrations act as his agent for all matters related to the pre-NDA meeting.

Responses to the questions posed by the sponsor were faxed to the sponsor on October 18, 2004.

**DISCUSSION:**

Responses to the questions posed by the sponsor.

QUESTIONS FOR FDA:

**CMC:**
The DS manufacturer and its process has been the same for the last 10 years, however the DP and its' manufacturer were different on two occasions during the clinical trial and will not be the same product that will be marketed post-approval.

We intend to show the comparability of these products by physico chemical means. Assuming we prove comparability, will the Agency allow the use of the accumulated clinical data using the same DS but different DP formulations to support a New Drug Application?
Q1: Will this be acceptable to the Agency?

**FDA Response:**

**In general, bridging studies should be conducted to show that the newly formulated drug product and the formulation used in clinical trials have the same dissolution and *in-vivo* / *in-vitro* correlation. Given the fact that your drug product (b) (4) may be very difficult to use this approach. However, we would be willing to discuss this further with you when these comparative data are available so that we can better advise you.**

Additionally, we intend to place the remaining 24 patients presently on study on the new formulation of DP (which will be used post-approval) and accumulate data while the NDA is being complied for submission. We anticipate to collect about 6 months of data in these patients and will submit this a further support of equivalency of the new DP formulation to the older products.
Q2: Does the Agency have any comment to this?

**FDA Response:**

**In addition, this may support comparability of these products with the physicochemical data.**

The DS and DP specifications are given in the submission.
Q3: Does the Agency have any comment to them? Are they acceptable?

**FDA Response:**

**No, they are not acceptable. See CMC additional comments.**

Two methods of analysis, an HPLC for assay testing and a TLC for (b) (4) testing are used for the DS and HPLC is used for the DP.
Q4: Are these methods acceptable to the Agency for their intended use?

**FDA Response:**

**No. The TLC method is used to provide qualitative data. Related substances must be determined using valid quantitative methods (e.g. HPLC) in addition to TLC. (See CMC additional comments)**

## CMC additional comments:

**Drug substance:**

- **Provide full characterization** (b) (4)
- **Clarify** (b) (4) **in the final product.**
- (b) (4) **specifications for related substances based on manufacturing batch data.**
- (b) (4) **specification for residual solvent** (b) (4) **based on manufacturing batch test data.**
- **Related substances must be determined using a quantitative method (e.g. HPLC) in addition to TLC.**

- **Establish tests in the drug substance specifications** (b) (4)
- **Develop a working reference standard for the drug substance** (b) (4)
- (b) (4) **issue should be further discussed at CMC meeting.**

**Drug Product:**

- **Specification** (b) (4) **must be determined using a quantitative method.**

**It is recommended that the sponsor should request a separate CMC EOP II/pre-NDA meeting.**

***The sponsor will request an EOP II/pre-NDA meeting for CMC prior to June 2005.***

**TOXICOLOGY:**
The Pharmacology and toxicology documentation presented is a summary of the literature on cholic acid use. Based on the fact that cholic acid is a natural component of the human body and the wealth of information on this subject, no additional toxicology studies are going to be performed.

Q5: Does the agency agree with this assessment?

**FDA Response:**

**Yes. We agree.**

**CLINICAL:**
Our clinical summary notes six inborn errors of bile acid synthesis and one secondary defect impacting bile acid synthesis. The documentation presented in this clinical summary describes patient data mostly in one enzyme defect and in the secondary defect impacting bile acid synthesis. In these two areas we have entered 60 patients with complete or partial data in 36 patients. In the other three areas that are the subject of this report (one defect is unresponsive to cholic acid therapy and one defect involves a conjugation defect, not the subject of this therapy) we have very limited results. In fact we have very limited data in nine out of 26 patients. See tables 1 and 2 in the report.

We also realize that this question is intricately tied to the points made related to Q1 and Q2, thus we appreciate the discussion and interaction within these two areas.

Q6: Considering the Orphan nature of this disease and its seriousness, as well as the fact that we have been treating all of these patients as they have been diagnosed (some

cases over 10 years), will the Agency consider this documentation sufficient to support a New Drug Application?

**FDA Response:**

**From our initial review of the information provided, it seems that an application might be supported for the use of cholic acid** (b) (4)

**The wording in the various sections of the labeling,** (b) (4) **is a review matter. For example, we would not anticipate approving the use of cholic acid** (b) (4)

**Additional Biopharmacology comments:**

**For a new drug application (NDA), we routinely require the sponsor to characterize pharmacokinetics of the drug product, including effect of intrinsic and extrinsic factors. The sponsor should consider providing this information in the NDA and justify as appropriate If some of the requirements are not applicable to this product.**

**CONLUSION:**

The sponsor will request an EOP II/pre-NDA meeting for CMC prior to June 2005.

**Minutes Preparer:** _____
Monika Houstoun, Pharm.D.
Regulatory Project Manager

**Chair Concurrence:** _____
Hugo Gallo-Torres, M.D., Ph.D.
Medical Team Leader

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/s/
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Monika Houstoun
11/18/04 05:31:07 PM

Hugo Gallo Torres
11/18/04 07:57:17 PM

# LATE-CYCLE COMMUNICATION DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**MEETING MINUTES**

Asklepion Pharmaceuticals, LLC
Attention: Gary Pasternack, MD, PhD
Chief Executive Officer
729 East Pratt Street
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) dated November 21, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for CHOLBAM (cholic acid Capsules) 50mg and 250mg.

We also refer to the Late Cycle meeting between representatives of your firm and the FDA on September 19, 2014.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-796-1008.

Sincerely,

*{See appended electronic signature page}*

Lara Dimick, M.D.
Medical Team Leader
Division of Gastroenterology and
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF LATE-CYCLE MEETING MINUTES

**Meeting Date and Time:** September 19, 2014 Noon – 1:30PM
**Meeting Location:** White Oak Building #22/Conference Room 5201 - Teleconference

**Application Number:** NDA 205-750
**Product Name:** Cholic Acid Capsules
**Applicant Name:** Asklepion Pharmaceuticals, LLC

**Meeting Chair:** Lara Dimick, M.D.
**Meeting Recorder:** Brian Strongin, R.Ph., MBA

## FDA ATTENDEES

| | |
|---|---|
| Julie Beitz, M.D. | Director, Office of Drug Evaluation III |
| Donna Griebel, M.D. | Director, Division of Gastroenterology and Inborn Errors Products (DGIEP) |
| Andrew Mulberg, M.D. | Deputy Director, DGIEP |
| Joyce Korvick, M.D. | Deputy Director for Safety, DGIEP |
| Lara Dimick, M.D. | Medical Team Leader DGIEP |
| Wen-Yi Gao, M.D. | Medical Officer, DGIEP |
| Sue-Chih Lee, Ph.D. | Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCP III) |
| Insook Kim, Ph.D. | Clinical Pharmacology Reviewer, DCP III |
| Ben Vali, M.S. | Statistical Reviewer, Office of Biometrics III |
| Ethan Hausman, M.D. | Medical Officer, Pediatric and Maternal Health Staff |
| David Joseph, Ph.D. | Pharmacology/Toxicology Team Leader, DGIEP |
| Ke Zhang, Ph.D. | Pharmacology/Toxicology Reviewer, DGIEP |
| Carolyn McCloskey, M.D. | Medical Officer, Division of Epidemiology III |
| Denise Pica-Branco, Ph.D. | Senior Regulatory Health Project Manager |
| Brian Strongin, R.Ph., MBA | Chief, Project Management Staff |

## SPONSOR'S ATTENDEES

| Name | Affiliation |
|---|---|
| Gary Pasternack, MD, PhD | CEO, Asklepion |

| | |
|---|---|
| Kellie Kennon, BSN | Director, Clinical Research, Asklepion |
| Kenneth Setchell, PhD | Professor, Cincinnati Children's Hospital and Medical Center |
| James Heubi, MD | Professor, Cincinnati Children's Hospital and Medical Center |
| (b) (4) | Consultant |
| (b) (4) | Consultant, (b) (4) |
| (b) (4) | Consultant, (b) (4) |
| (b) (4) | Consultant, (b) (4) |
| (b) (4) | Consultant, (b) (4) |
| (b) (4) | Consultant, (b) (4) |

**BACKGROUND**

NDA 205750 was submitted November 21, 2013 for CHOLBAM (cholic acid) Capsules.

Proposed Indication: (b) (4)

PDUFA Goal Date: October 21, 2014

FDA issued a Background Package in preparation for this meeting on September 4, 2014.

**DISCUSSION**

**Substantive Review Issues - Clinical**

The following substantive review issues have been identified to date:

1. The use of change in atypical urinary bile acids as the primary efficacy endpoint:

   FDA has concerns regarding the acceptability of quantified atypical urinary bile acid in assessing the efficacy of cholic acid treatment for the following reasons:

   - You have not established that a reduction in atypical urinary bile acids is a surrogate that is likely to predict clinical outcomes.

   - The bioanalytical assay method for detecting atypical urinary bile acids is not adequately validated to the regulatory standard to support quantitative assessment of its use as a prognostic biomarker. (b) (4)

*Discussion*

*The sponsor stated that urinary bile acids, at present, are an aid to diagnosis only and that it will take about 1 year to develop a validated assay. The sponsor added that they have submitted a full validation package for an LCMS method that showed a correlation between the LCMS and FAB-MS assays.*

*The Agency responded that they have seen the validation data on the LCMS method that had been submitted to the NDA. Those data can't be considered as quantitative for review purposes.*

*The Agency agreed that the FAB-MS method is acceptable for diagnosis* (b) (4)

*The sponsor stated that the primary goal of cholic acid therapy is to shut down bile acid synthesis and decrease levels of atypical bile acids.* (b) (4)

(b) (4)

(b) (4)

*Division stated information on dose adjustment would need to be obtained as part of the post marketing registry* (b) (4)

*The sponsor stated that they felt that clinicians would continue to send urine samples to the investigators lab for analysis of atypical bile acids* (b) (4)

2. Dose and dose adjustment:

You have proposed a dose range of 10-15 mg/kg; however, the doses in the trial widely varied from 3.3 to 26 mg/kg on day 1, and from 3.27 to 24.56 mg/kg for the last documented dose. Documentation of the rationale for dosage adjustment, i.e., relevant clinical observations and/or biomarkers (e.g., transaminases, bilirubin) is not adequate for our review.

You have proposed [redacted] (b) (4)

FDA is also concerned about the use of unvalidated assay methodologies [redacted] (b) (4)

*Discussion: see above*

3. You have not provided convincing evidence that cholic acid is effective for the peroxisomal disorder (PD) population:

- The mean of total bilirubin in PD patients, calculated from median Baseline to median post-treatment (n=25) worsened from 1.495 to 1.621 mg/dL (Sequence number 020, May 6, 2014)
- The median of weight percentile medians of patients with Zellweger's disease from median baseline to median post-treatment (n=11) worsened from 5.83 to 0.18 (Sequence number 028, July 11, 2014)
- The median of weight percentile medians of neonatal adrenoleukodystrophy (NALD) worsened from 1.76 to 0.40 (Sequence number 028, July 11, 2014)
- There were 12 PD patients who had both pre- and post-treatment liver biopsies: 7 of the 12 patients had no change in inflammation (lobular or periportal), fibrosis, necrosis, or cholestasis, while 5 of the 12 patients had evidence of worsened liver histopathology.
- The death rate of PD patients on cholic acid treatment was high (48%, 14/29).
- Seven of the 14 PD patients who died during treatment had abnormal liver transaminases, abnormal serum bilirubin, or cholestasis on liver biopsy on post-treatment evaluations. Some of these patients did not have pre-treatment evaluations presented, making assessment difficult. However, the potential of cholic acid treatment-induced hepatic injury cannot be excluded.
- The atypical urinary bile acid levels do not appear to correlate with clinical outcomes. This is especially noted in the PD population. We note that 6 of the 7 PD patients who died had post-treatment urinary bile acid levels interpreted as normal or a score of zero.

*Discussion:*

*The Agency commented that, although there have been a few successes, we can't point to differences between those PD patients that survived and those that didn't.*

*The sponsor responded that the only problem with SED patients is a problem with the bile acid synthesis pathway. Administering a normal pool of bile acids is curative in those patients.*

*PD is a multi-organ disease. PD patients can't perform beta oxidation. Liver disease involves abnormal bile acids and is a principle cause of early morbidity and mortality in PD patients. Suppressing abnormal bile acid synthesis leads to normal bile acids. No treatment exists for the other symptoms of PD. PD patients have neurological defects in addition to liver and other defects. Cholic acid only treats the liver disease. Although PD patients with advanced liver disease are unlikely to respond, less severe patients are likely to respond.*

*The Agency asked the sponsor to submit information about patients that were less severe and may have been helped by Cholic Acid and how they were helped.*

*The Agency commented that any labeling for PD patients would have to reflect that the course of the disease is unlikely to change.*

*The Agency asked the sponsor to explain why some patients were successes and how they were different from the failures?*

*The Agency asked if after approval, the LCMS assay on urinary bile acids would be utilized in the investigators lab for analysis of atypical urinary bile acids.*

(b) (4)

*At this time, the older assay will be used by the investigatory in their lab.*

**REVIEW PLANS**

After receiving the individual patient narratives and graphical patient profiles requested August 21, 2014, we plan to complete the clinical review, labeling mark-up, and take an appropriate action. However, due to the multiple deficiencies encountered in the original NDA submission, e.g., the lack of a systematic approach to the collection and recording of efficacy data, and the lack of a pre-defined dosing algorithm, FDA has needed to rely on numerous information requests to try and fill in the data gaps. For this reason, we anticipate that the action date for this application will be delayed. We will notify you of a target date by which we anticipate that we can complete our review after we have received all of the responses to our information requests.

*Discussion:*

*The Agency explained that they are aiming for an action by 12/1/14. We need to analyze the narratives. The information we've requested will help us understand the narratives.*

**WRAP-UP AND ACTION ITEMS**

This application has not been fully reviewed by the signatory authority, division director, and the Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not attress the final regulatory decision for this application.

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/s/

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LARA DIMICK-SANTOS
12/16/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205750

**LATE CYCLE MEETING**
**BACKGROUND PACKAGE**

Askelpion Pharmaceuticals, LLC
Attention: Gary R. Pasternack, M.D., Ph.D.
Chief Executive Officer
729 E. Pratt Street
Suite 360
Baltimore, MD 21202

Dear Dr. Pasternack:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cholic Acid Capsules, 50mg and 250mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for September 19, 2014. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Brian Strongin, R.Ph., MBA, Chief Regulatory Project Management Staff, at (301) 796-1008.

Sincerely,

*{See appended electronic signature page}*

Andrew E. Mulberg, M.D.
Deputy Director
Division of Gastroenterology and
Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Late-Cycle Meeting Background Package

## LATE-CYCLE MEETING BACKGROUND PACKAGE

**Meeting Date and Time:** September 19, 2014 Noon – 1:30PM
**Meeting Location:** White Oak Building #22/Conference Room 5201 - Teleconference

**Application Number:** NDA 205-750
**Product Name:** Cholic Acid Capsules
**Indication:** (b) (4)

**Sponsor/Applicant Name:** Asklepion Pharmaceuticals

## INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

## BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

### Discipline Review Letters

No Discipline Review letters have been issued to date.

### Substantive Review Issues - Clinical

The following substantive review issues have been identified to date:

1. The use of change in atypical urinary bile acids as the primary efficacy endpoint:

   FDA has concerns regarding the acceptability of quantified atypical urinary bile acid in assessing the efficacy of cholic acid treatment for the following reasons:

(b) (4)

2. Dose and dose adjustment:

You have proposed a dose range of 10-15 mg/kg; however, the doses in the trial widely varied from 3.3 to 26 mg/kg on day 1, and from 3.27 to 24.56 mg/kg for the last documented dose. Documentation of the rationale for dosage adjustment, i.e., relevant clinical observations and/or biomarkers (e.g., transaminases, bilirubin) is not adequate for our review.

You have proposed (b) (4) FDA is also concerned about the use of unvalidated assay methodologies (b) (4)

3. You have not provided convincing evidence that cholic acid is effective for the peroxisomal disorder (PD) population:

- The mean of total bilirubin in PD patients, calculated from median Baseline to median post-treatment (n=25) worsened from 1.495 to 1.621 mg/dL (Sequence number 020, May 6, 2014)
- The median of weight percentile medians of patients with Zellweger's disease from median baseline to median post-treatment (n=11) worsened from 5.83 to 0.18 (Sequence number 028, July 11, 2014)
- The median of weight percentile medians of neonatal adrenoleukodystrophy (NALD) worsened from 1.76 to 0.40 (Sequence number 028, July 11, 2014)
- There were 12 PD patients who had both pre- and post-treatment liver biopsies: 7 of the 12 patients had no change in inflammation (lobular or periportal), fibrosis, necrosis, or cholestasis, while 5 of the 12 patients had evidence of worsened liver histopathology.
- The death rate of PD patients on cholic acid treatment was high (48%, 14/29).
- Seven of the 14 PD patients who died during treatment had abnormal liver transaminases, abnormal serum bilirubin, or cholestasis on liver biopsy on post-treatment evaluations. Some of these patients did not have pre-treatment evaluations presented, making assessment difficult. However, the potential of cholic acid treatment-induced hepatic injury cannot be excluded.

- The atypical urinary bile acid levels do not appear to correlate with clinical outcomes. This is especially noted in the PD population. We note that 6 of the 7 PD patients who died had post-treatment urinary bile acid levels interpreted as normal or a score of zero.

**REMS OR OTHER RISK MANAGEMENT ACTIONS**

No issues related to risk management have been identified to date.

**Pre - LCM AGENDA**

1. Introductory Comments – 5 minutes (RPM/CDTL)

   Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Substantive Review Issues – 60 minutes

   Each issue as noted above will be introduced by FDA and followed by a discussion.

3. Additional Applicant Data – 5 minutes (Applicant)

4. Information Requests – 5 minutes

   Clinical


Cholic Acid 8-14 Clinical IR.p...


Cholic Acid IR 8-21-14.pdf


8-28-14 Cholic Acid Clinical L..

5. Review Plans – 5 minutes

   After receiving the individual patient narratives and graphical patient profiles requested August 21, 2014, we plan to complete the clinical review, labeling mark-up, and take an appropriate action. However, due to the multiple deficiencies encountered in the original NDA submission, e.g., the lack of a systematic approach to the collection and recording of efficacy data, and the lack of a pre-defined dosing algorithm, FDA has needed to rely on numerous information requests to try and fill in the data gaps. For this reason, we anticipate that the action date for this application will be delayed. We will notify you of a target date by which we anticipate that we can complete our review after we have received all of the responses to our information requests.

6. Wrap-up and Action Items – 5 minutes

| | |
|---|---|
| **From:** | Barley, Stacy |
| **To:** | "kellie.kennon@asklepionpharm.com"; "gary.pasternack@asklepionpharm.com" |
| **Subject:** | FW: NDA 205750 Cholbam (cholic acid): Information Request |
| **Date:** | Thursday, August 14, 2014 4:22:00 PM |
| **Attachments:** | NDA 205750 cholic acid Tables.doc<br>NDA 205750 cholic acid Tables.pdf |

Hello:

Please refer to your New Drug Application (NDA) dated and received November 21, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, for Cholbam (cholic acid) capsules, 50 mg and 250 mg.

We are in the process of reviewing your application and request additional information. Please complete the attached document.

We request a response by close of business August 19, 2014. Contact Brian Strongin on or after August 18th if you have any additional questions.

Thank you.

*Stacy Barley, RN, M.S.N., M.S.H.A.*

*CDR, USPHS Commissioned Corps*

*Senior Regulatory Project Manager*

*Division of Gastroenterology/Inborn Errors Products*

*Office of Drug Evaluation III*

*CDER/FDA*

*(301) 796-2137 (office)*

*(301) 796-9905 (fax)*

*stacy.barley@fda.hhs.gov*

NDA 205750 cholic acid

August 14, 2014

**DGIEP Information Request:** Provide the appropriate outcomes to the corresponding space in the following two tables. DGIEP will evaluate the responder responses in ALT reduction and related changes of bilirubin, weight percentile, survival time, and treatment duration. If you do not have the data, provide explanations.

**SED Patients on Cholic Acid**

| ALT reduction from baseline | N (%) | Bilirubin change (mean, range) | Weight change (mean, range) | Survival (mean, range) | Treatment duration (mean, range) |
|---|---|---|---|---|---|
| At least 25% | X (x%) | | | | |
| At least 50% | Y (y%) | | | | |
| At least 75% | Z (z%) | | | | |

**PD Patients on Cholic Acid**

| ALT reduction from baseline | N (%) | Bilirubin change (mean, range) | Weight change (mean, range) | Survival (mean, range) | Treatment duration (mean, range) |
|---|---|---|---|---|---|
| At least 25% | X (x%) | | | | |
| At least 50% | Y (y%) | | | | |
| At least 75% | Z (z%) | | | | |

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/s/

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STACY R BARLEY
08/14/2014



Reference ID: 3622126

| | |
|---|---|
| **From:** | Strongin, Brian K |
| **To:** | gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com |
| **Cc:** | Strongin, Brian K |
| **Subject:** | Information Request for NDA 205-750 Cholic acid |
| **Date:** | Thursday, August 21, 2014 9:28:28 AM |

Please respond to this information request no later than September 12, 2014. The information we are requesting now is included in the August 18 information request, so you can just ignore that one and provide everything in this one. You can give it to us in groups by subtype as you finish them so we can evaluate the data faster.

> Provide individual patient narratives for all patients in your application for whom you have not previously submitted a narrative. Identify each patient by subtype of disorder, and group narratives by subtype. Provide pre-treatment baseline information on dose, start date, dose changes, and concomitant medications, including ursodeoxycholic acid (URSO), physical exams, clinical course, and outcome. For peroxisomal disorder (PD) patients, include neurological exams and documentation of improvement or decline in neuro-cognitive function, and very long-chain fatty acids (VLFA) at baseline and follow-up.
> For each graphical patient profile, display data for ALT, AST, Bilirubin total and direct, urine bile acid evaluations, and growth in height and weight over time. Indicate start and stop dates for cholic acid (and URSO) on the graphs.

Thanks and let me know if you have any questions.

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/s/

BRIAN K STRONGIN
08/21/2014

**From:** Strongin, Brian K
**To:** gary.pasternack@asklepionpharm.com; kellie.kennon@asklepionpharm.com
**Cc:** Strongin, Brian K
**Subject:** Clinical Information Request
**Date:** Thursday, August 28, 2014 10:29:11 AM

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Please respond to this information request ASAP.

Please provide information about the registry you have in Europe for Cholic Acid. Provide the protocol and a summary of any data that have been collected to date.

Thanks.

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/s/

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BRIAN K STRONGIN
08/28/2014

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/s/

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ANDREW E MULBERG
09/04/2014